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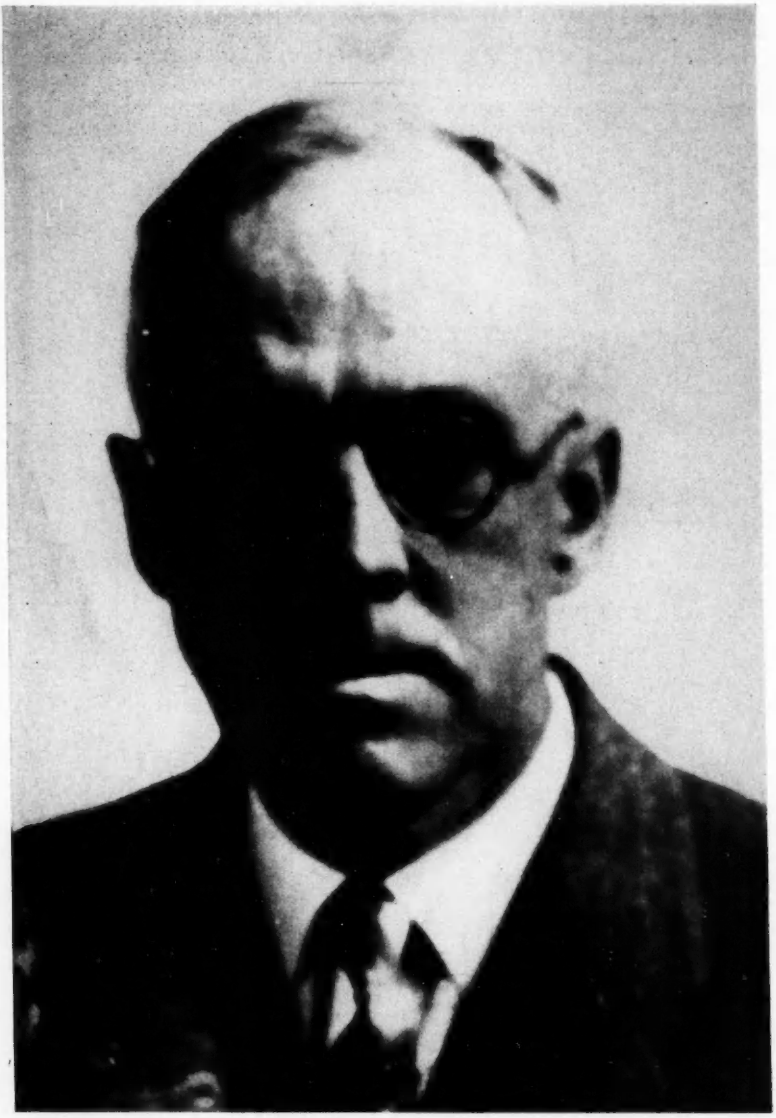

OBITUARY

DR. WILLIAM P. WILLARD

John Ruskin said: "I believe the first test of a truly great man is humility." In my long association with Doctor Willard I never encountered a man who was so totally self-effacing and lacking in personal conceit. He left no diary or personal notes, not even a photograph for posterity to keep alive his memory, except a very inadequate passport snapshot which was a necessary formality incidental to his travel in foreign countries.

Doctor Willard was born in Oakland, California, February 20, 1877 of Scotch-English parents from New Brunswick, Canada. He graduated from the University of California School of Medicine in 1899. He was a classmate of one of the revered members of the American Association of Genito-Urinary Surgeons, Dr. William E. Stevens of San Francisco who has now passed his eightieth year. Doctor Willard served his internship at the French Hospital in San Francisco. The next year was spent as surgeon to the Alaska Packers Salmon Fisheries in Alaska. This was followed by a year in the copper mines in Arizona.

He then became interested in urology as a specialty and spent some time at the Johns Hopkins Hospital in Baltimore. There he became well acquainted with Dr. Hugh H. Young at the inception of his meteoric career in that institution.

Shortly thereafter he returned to San Francisco and became associated with Dr. Martin Krotoszyner who was connected with the old German (now Franklin) Hospital. Doctor Krotoszyner belonged to the vanguard of pioneer urologists in this country. His promising career was cut short by an assassin's bullet in his office.

Doctor Willard became professor of urology of the University of California and remained as chief of that department until 1914. He continued in private practice as chief of the department of urology at St. Luke's Hospital. He was a dominant figure in West Coast urology until his retirement in 1929.

After two years spent touring European countries with his family he grew restive and returned to San Francisco to resume practice. We shared offices from that time until his second retirement in 1941. This association proved to be a very happy and fortunate one for me, and I shall always remain deeply grateful and indebted to him for his words of wisdom and example.

Following his second retirement he bought a ranch in the beautiful Napa Valley near the town of St. Helena, about seventy miles north of San Francisco. With the outbreak of World War II, we prevailed upon him to return to San Francisco and help us out on the overburdened urological service of the Southern Pacific Railroad Hospital. Here he did a magnificent job until the termination of the war, when he retired for the third and last time. He loved to travel, so during both his active and retired years he visited all corners of the globe until his final illness forced him to remain at home in San Francisco, where he succumbed on April 6, 1955, at the age of seventy-eight.

He is survived by his widow, Myrtle McCartney Willard, and two children, a son, Oliver, who is professor of English at the University of Oregon, and a daughter, Mignon (Mrs. Arnold Bradley) of Carmel, Calif.

He became a member of the American Association of Genito-Urinary Surgeons in 1937.

I am grateful for the privilege of writing this brief obituary, because he was a friend of long standing, for whom I developed an ever increasing affection and admiration. In personal deportment and dress he was the embodiment of professional neatness and dignity. He was outspoken to the point of bluntness, with an honesty of character and integrity that were exemplary and above reproach. He was truly a great man.

Thomas E. Gibson

PRESENTATION OF THE KEYES MEMORIAL MEDAL TO DR. CHARLES C. HIGGINS

DR. THOMAS D. MOORE

Memphis, Tenn.

"Reason and calm judgment, the qualities specially belonging to a leader."
—Tacitus, History, Bk. III, Sec. 20

Charles C. Higgins: Author, scientist, teacher and urological surgeon of renown, you have been chosen by your confreres in this Association for about the highest honor it can confer, the award of the Keyes Memorial Medal. Twenty-three years ago the Keyes Medal was presented for the first time to Dr. Alfred Newton Richards of Philadelphia; only six others have been similarly honored. This is indeed a select group, the names of whom are bywords in the field of urology, and their contributions to urological progress will live down through the ages. Since the original award of the medal to Dr. Richards, presentations have been made to the following: Dr. Edward L. Keyes, Jr., 1936; Dr. Hugh H. Young, 1937; Dr. Henry G. Bugbee, 1944; Dr. Herman L. Kretschmer, 1950; Dr. William F. Braasch, 1951; and Dr. Frank Hinman, Sr., 1954. What characteristics do these recipients of the award have in common which justified such recognition? One might mention meritorious work, keen observation, originality, unwavering integrity in the recording of procedures and results, and a desire for others to profit from one's experience, which of itself greatly stimulates contributions to scientific literature. You have abundantly displayed all of those traits with which this group is endowed and a review of your achievements through the years furnishes convincing evidence that you are deserving of this canonization, so to speak, and that you should be numbered among the truly great urologists.

You were fortunate in acquiring an excellent fundamental education. You received the Bachelor of Science degree from the University of North Dakota in 1919 and in 1923 you were awarded the degree of Doctor of Medicine from Washington University, St. Louis, Missouri. After serving your internship at Washington University Clinics and later at the Lakeside Hospital, Cleveland, Ohio, you completed your residency training in surgery and urology at the Cleveland Clinic Foundation Hospital in 1928 under the guidance and influence of the late Dr. William E. Lower. Evidently he recognized the diligence of your work, your inquisitive mind, and your bent for research, which prompted your retention on the permanent staff of the Cleveland Clinic. Your brilliant career has more than justified Doctor Lower's judgment.

Your contributions to urological literature number 165, about one-third of which have dealt with some aspect of urolithiasis. In 1933 you made your original report on the experimental production of urinary calculi and your subsequent experimental work, with particular reference to vitamin A deficiency, was received with widespread interest. In 1933 you originated a technique for aseptic ureterointestinal anastomosis and through the years you have published 24

articles dealing with ureterosigmoidostomy incident to exstrophy of the bladder and cystectomy for carcinoma. You pointed out the advantages of the early surgical treatment of exstrophy of the bladder in young infants and argued against delay of the operation until an older age with the delay often permitting serious renal complications incident to infection. In 1934 you were the first to perform on the human a transuretero-ureterostomy, when a painful refluxing ureter was transplanted to the opposite one, thus conserving the involved k dney by taking advantage of the intact valve on the opposite side; the courage of your conviction in performing this operation was justified by the highly satisfactory clinical result. Your contributions have touched upon nearly all phases of clinical urology and are frequently referred to in the literature. You were the author of the outstanding monograph published in 1943, Renal Lithiasis. In 1939 you published the history of the American Association of Genito-Urinary Surgeons and in 1954 you contributed the chapter on Urolithiasis in Campbell's Urology.

You have exerted a great and beneficial influence not only from a scientific standpoint but on organizational phases of American urology. You have always been insistent upon the maintenance of high standards; this has been especially evident in the programs of the American Association of Genito-Urinary Surgeons. A perusal of the list of urological organizations with which you have been affiliated indicates that almost without exception you have been elevated to their highest office. You served this organization as secretary from 1938 to 1947 and were elected president in 1951. You were secretary of the Clinical Society of Genito-Urinary Surgeons from 1940 to 1946 and were president in 1948. You were president of the Cleveland Urological Society in 1937. You were president of the North Central Section of the American Urological Association in 1939. You were president of the American Urological Association in 1949. You were president of the American Urological Research Foundation, Inc. in 1953. You were chairman of the Section on Urology of the American Medical Association in 1955. You were a member of the American Board of Urology, Inc. for 15 years. In the affairs of the American College of Surgeons your influence for the good of urology is well known. You have rightfully contended for better recognition of the surgical specialties and were elected chairman of the Board of Governors in 1955. In fact, the honors that you have received are international in scope and include honorary memberships in urological societies in Italy, Venezuela and Puerto Rico.

Although your urological schedule has been a crowded one, you have found time for a diversification of interests with special reference to wholesome recreation and cultural pursuits. Not only have you been a true lover of music but you have favored others by your own talented performance on the piano. In literature you have acquired a marvelous library, including probably the largest collection of the works of Goldsmith extant.

Charlie Higgins: Truly your career has been a great one for outstanding achievements and for the beneficent influence you have exerted on American urology. It is fitting indeed that you have been chosen as recipient of the Keyes Memorial Medal. I consider it a distinct honor and a genuine pleasure to make this award today. It is a token of the very high esteem and affection with which you are held by the members of the American Association of Genito-Urinary Surgeons.

A SIMPLIFIED TECHNIQUE FOR CYSTECTOMY AND REPAIR OF THE ABDOMINAL DEFECT IN EXSTROPHY OF THE BLADDER

HARRY M. SPENCE

From the Department of Urology of the Dallas Medical and Surgical Clinic and The University of Texas Southwestern Medical School, Dallas, Texas

Renewed efforts to close the exstrophic bladder and construct a sphincter mechanism in order to avoid the obvious shortcomings of ureterointestinal anastomosis in this condition are most commendable, and are yielding promising preliminary results. The same may be said for the carefully thought out concept of Boyce and Vest in which a permanent colostomy is combined with anastomosis of the trigone to the isolated rectal pouch. However, until such techniques are further perfected and their superiority proved by a substantial number of cases assessed in the light of long-term results, I believe that the current treatment of exstrophy should continue to be bilateral ureterosigmoidostomy, removal of the bladder, and correction of the associated external genital defects. Indeed, experience in recent years with transplantation of the ureters to the sigmoid, carried out within the first year of life, has been quite acceptable and far superior to the results obtained in years past at a corresponding period of postoperative followup. While no one can say that the results will continue satisfactory indefinitely, the trend to date warrants continuance until a proved better method is developed.

The object of this paper, then, is to present the operative technique for removal of the bladder and repair of the abdominal wall defect after the ureters have been successfully transplanted to the bowel.

In contrast to the multitude of articles dealing with the technique of ureterointestinal anastomosis, there is comparatively little in the literature regarding the technique of bladder removal in exstrophy. Three different principles have been utilized: 1) the development of flaps from the rectus fascia to cover the triangular defect in the lower abdominal wall after the entire bladder has been removed; 2) the use of tantalum mesh to bridge the defect again after removal of the entire bladder; and 3) removal of the bladder mucous membrane only with preservation of the fibromuscular wall and utilization thereof in closure of the defect. The technique to be presented is of the latter type.

Hutchins and Hutchins[1] in 1923 published a detailed description of the use of overlapping fascial flaps to close the defect. This method is fairly satisfactory but involves extensive dissection, and on the few occasions where I have seen it used there has always been a certain amount of slough and slow healing. Strong[2] (1950) presented a case in which he used tantalum mesh to bridge an extensive defect in an adult who had undergone several previous attempts at closure of the abdominal wall defect. Postoperatively the result seemed excellent

[1] Hutchins, E. H. and Hutchins, A. F.: Exstrophy of bladder with successful transplantation of ureters into rectum. Surg., Gynec. & Obst., **36:** 731, 1923.

[2] Strong, G. H.: Repair of large abdominal defects following cystectomy for congenital vesical exstrophy: A new technique. J. Urol., **64:** 743, 1950.

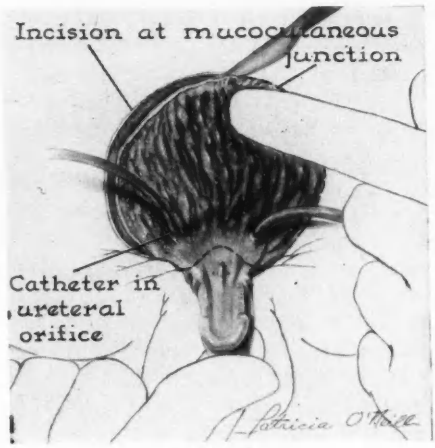

FIG. 1

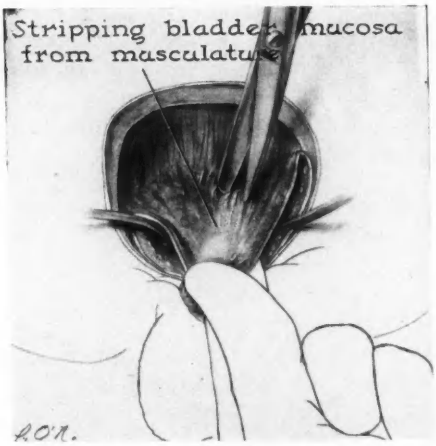

FIG. 2

and undoubtedly such material may be necessary in an occasional case, particularly in the older age group. However, it would be unnecessarily complicated if the same result can be obtained by a simpler measure. In 1951 Hepburn[3] presented his method of reconstruction in which he removed the bladder mucous membrane with a sharp curette, thereafter excising any excess fibromuscular bladder wall and suturing the cut edges. The denuded operative surface was then closed over by drawing together the undermined skin margins after making lateral relaxing incisions which require skin grafting. Gross[4] states that it is necessary only to remove the mucous membrane and tuck the bladder wall back

[3] Hepburn, T. N.: Repair of exstrophy of the bladder. J. Urol.., **65**: 389, 1951.
[4] Gross, R. E.: Surgery of Infancy and Childhood. Philadelphia: W. B. Saunders Co., 1953, p. 697.

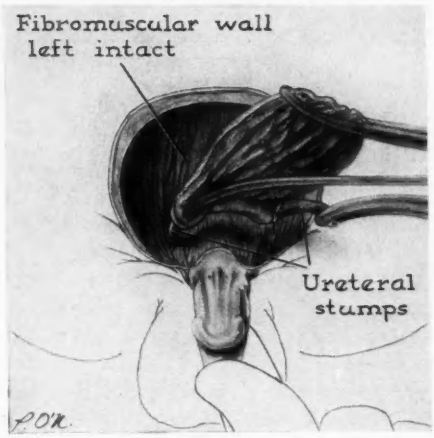

FIG. 3

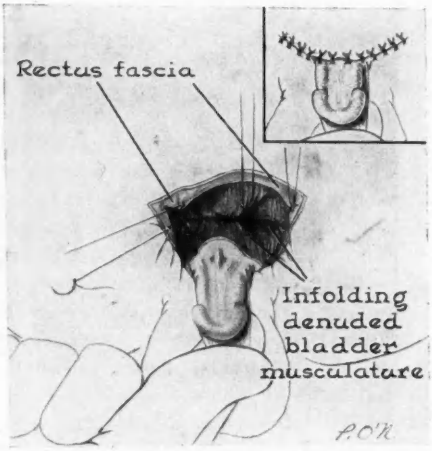

FIG. 4

in the defect which is closed by drawing the rectus muscles and fascia together in the midline.

The principle of the method to be presented is essentially that suggested by Hepburn, the differences being that 1) the bladder mucous membrane is dissected away by sharp dissection rather than relying on currettement and 2) the excess bladder wall is infolded for its additional tamponade effect rather than being excised. The time at which this will be carried out depends on the smoothness of convalescence after the ureteral transplant and the general condition of the infant. If all goes well the bladder may be removed about two weeks after the transplant but preferably six or eight weeks thereafter.

The details of the procedure (figs. 1–4) are as follows:

1) After preparation of the surrounding skin, bladder mucous membrane and external genitalia with pHisoderm, an incision is made with the scalpel about the entire circumference of the bladder wall at the mucocutaneous junction. As this circumscribing incision approaches the bladder neck, or rather the floor of the urethra, care is taken particularly in the male to avoid damage to underlying prostate and ejaculatory ducts.

2) The plane of cleavage between the bladder mucosa and the underlying fibromuscular structure is found, and by blunt and sharp dissection the entire mucosa is stripped off and discarded. Bleeding is controlled by gauze pressure except for arterial spurters which are tied. Where the mucosa is adherent to the underlying tissue, it is removed by sharp dissection. One need not be overly meticulous, as the objective is simply to remove all mucosa and leave the bulk of the bladder wall behind. As the dissection approaches the ureteral orifices, each blind ureteral stump is removed intact.

3) The denuded bladder wall is next inverted by progressive rows of chromic catgut sutures, which infold the tissues and serve to plug the defect between the diverging lower recti. These rows of sutures are taken transversely and one is surprised to note how the upper fascial rim of the defect is drawn downward, forming an additional closure layer.

4) The skin is closed transversely after minimal undermining of its margins. In several cases I have closed the skin under moderate tension with subsequent cutting out of the stitches but any raw surface has epithelialized with surprising rapidity and skin grafts have not been necessary.

5) In the male, the upper chordee of the epispadiac penis is corrected at this stage in similar fashion to the correction of the downward chordee in the hypospadiac penis by the Nesbit buttonhole technique (to be the subject of a later communication).

The technique has been used in 14 cases (9 male and 5 female patients). The resulting abdominal wall has been strong and solid in all, and the cosmetic result has been quite satisfactory.

SUMMARY

A simplified technique for cystectomy and closure of the abdominal defect in exstrophy of the bladder is presented. The essentials of the operation are removal of the mucosa and utilization of the infolded bladder musculature to aid in reconstructing the abdominal wall.

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RECONSTRUCTION OF URINARY BLADDER IN CHILDREN WITH EXSTROPHY

JOHN K. LATTIMER, ARCHIE L. DEAN, JR., CLEMENT FUREY AND LLOYD BALLANTYNE

From the Squier Urological Clinic and the Department of Plastic Surgery, Columbia University and Presbyterian Hospital, New York 32, N. Y.

In the treatment of exstrophy of the urinary bladder, Sweetser's modification of the Mikulicz operation for reimplanting the bladder into the abdomen has attracted great interest among both the physicians and parents of these unfortunate children. Previous techniques for dealing with this condition, utilizing ureteroenterostomy in various modifications, have left a great deal to be desired. For instance, in some children the anal sphincter was not competent to retain urine. In others there was a prolapse of the rectum. Strictures at the point of anastomosis between the ureter and the bowel were all too common. Infection and acidosis were constantly in the offing. We were therefore happy to try this new technique when Dr. Sweetser demonstrated its feasibility.

TECHNIQUE

Like Dr. Sweetser, we free up bladder and urethra, infolding them into a sac and tube. We free up a strand of muscle and fascia from the top edge of the pelvic diaphragm and wrap this strand around the new urethra at the bladder neck. In males we transplant the urethra to the bottom of the penis. The prepuce may be used as a tube to make the urethra reach the tip of the penis. A suprapubic cystostomy tube is left in place for 2 weeks. A suture through the perineum, to hold the bladder down, does not appear to be necessary. It is certainly not desirable to free up the bladder too much, lest the blood supply be damaged, or the ureters kinked.

The fascial defect is bridged by flaps of anterior rectus sheath, and the skin closure is done in a series of Z plasties by the Department of Plastic Surgery.

RESULTS

We have done seven of these operations and we have observed the results in 1 case done by Dr. Ralph Yeaw and 5 cases done by Dr. Sweetser. Ten were males and three were females. In ten the operative procedures have been completed. None are continent, although they are all below the expected age for continence. All can accumulate urine in the bladder and eject it, in addition to dribbling almost constantly. Bladder capacities average 75 cc. Four out of eight had urethral strictures which required dilatation. Reflux is present in most of the ureters, but appears to be a feature of the exstrophic ureter rather than of this technique. In those cases in the past in which the ureteral orifices were transplanted into the bowel, reflux has occurred in over half of our cases.

OPTIMUM AGE

The optimum age for this operation appears to us to be somewhere in the vicinity of six months. If one waits longer the bladder wall may become covered

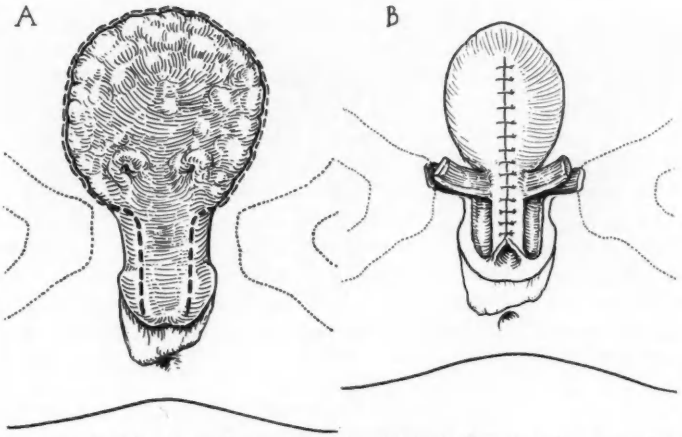

FIG. 1. *A*, an incision is made around exstrophied bladder and along margins of open urethra. This incision is deepened until all thicknesses of bladder wall and urethera can be freed from surrounding tissues sufficiently to form a sac and tube.

B, After bladder and urethra have been formed, a strand of muscle is liberated from top margin of the incomplete triangular ligament. This strand of muscle is raised on each side so that two halves can be joined around urethra near bladder neck. This muscular connection with pelvic diaphragm may provide some sphincteric action later.

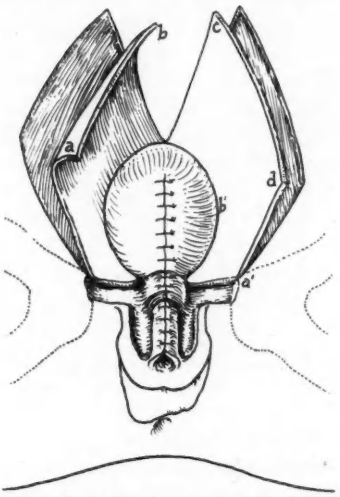

FIG. 2. After bladder and sphincteric ring have been formed, flaps of anterior rectus sheath are raised on each side. These flaps are used to cover bladder like two sides of double breasted coat. Their lower margins are sutured to top of incomplete pelvic diaphragm and to margin of new sphincteric ring.

with thickened granulation tissue to the point where it can not be inverted to make a reservoir of satisfactory size. We have done this operation at various ages ranging from 3 months to 3 years and the younger children appear to have done better. If the bladder is too small, either originally or as a result of granu-

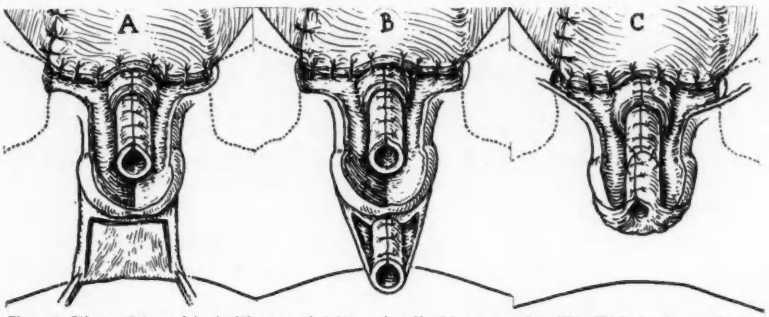

FIG. 3. Flap of foreskin is liberated (*A*) and rolled into a tube (*B*). This is drawn into end of open penis and joined with incomplete urethra. (*C*) This maneuver does away with strictures at meatus, and lessens incidence of pinhole fistulas along the dorsum of penis.

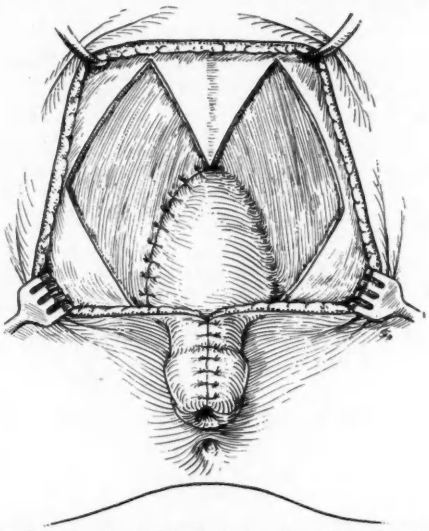

FIG. 4. New urethra is transplanted to bottom of penis and subcutaneous tissues and skin are brought together above urethra. Skin of abdomen is undermined by plastic surgical methods and brought together over midline in whatever design appears optimum for each case.

lations and contraction, we still attempt to roll it in upon itself. In one patient, where the bladder was extremely small, the bladder size increased to satisfactory dimensions after the operation, but hydroureter developed. This may have been due to stricture of the urethra rather than to the small bladder capacity. Nevertheless, this appears to be a technical hazard. If the bladder is large and flexible, there is less need to do the operation early.

DISADVANTAGES OF TECHNIQUE

This is a formidable operative procedure from the point of view of operating time. In most of our cases some eight hours were required for the operation,

with the urologist working on the urinary tract for three or four hours and the plastic surgeons then coming in to work for three or four more hours to close the skin in a satisfactory fashion. The length of time involved, with these tiny children, sometimes made it advisable to do the operation in stages; the bladder portion being done first, down to the creation of the sphincter, with the penile portion being done later, in the male children. Strictures and pinhole fistulas along the dorsum of the new penis are a hazard, but since these are technical matters, they can be overcome with experience.

The principal concern in regard to this operation is the uncertainty as to whether or not the sphincter mechanism will work. Since none of our children has as yet reached an age when he or she might be actively interested in cooperating to achieve continence, it is impossible to estimate whether or not any will ever have satisfactory urinary control. They are definitely below par for their age group at this time, but we have been so encouraged by the success of voluntary efforts on the part of patients with epispadias, to control their urine, that we have some hope that these children can achieve control in later life. The possibility also exists that the continuing lateral growth of the child will pull open the newly-formed urethra, especially in the young female patients.

ADVANTAGES OF TECHNIQUE

The advantages of this technique are considerable. First of all it is a safe operation. It is primarily superficial and there are no dangerous intraperitoneal points of union where urine might leak, as in the techniques employing ureteroenterostomy. Secondly, we are not plagued with either acidosis or infection to any extent. There is no increased opportunity for strictures of the ureters since there are no new anastomoses between the ureters and the bowel. This technique more nearly duplicates Nature's own pattern for the design of the urinary tract. This is most appealing to the parents of these children, who would a thousand times rather have an attempt at restoration in the direction of normalcy, rather than a transplantation of the ureters into the intestine. Lastly, this technique is revocable. Nothing has been lost and nothing has been destroyed by an attempt at this operation. The ureters can still be transplanted into the intestine, into a segment of ileum or into the skin, as before, if this technique does not prove practical.

We have had occasion to compare the effectiveness of the Coffey 1, the Leadbetter, the Madl and the Goodwin techniques, with and without colostomy, in substantial series of cases. It is our current view that this new technique is worthy of evaluation and that all children with exstrophy should have the benefit of at least one attempt to infold the bladder back into the abdomen, by this new method.

USE OF ANTEROPUBIC FASCIAL SLING FOR TREATMENT OF SURGICAL INCONTINENCE IN THE MALE

CHARLES A. W. UHLE

From the Department of Urology, Lankenau Hospital, Philadelphia, Pa.

This presentation will summarize my experience and thoughts pertaining to the fascial sling placed anterior to the pubis and about the bulbous urethra for the control of urinary incontinence. Ten and one-half years have elapsed since the first case was operated upon. A total of 8 cases form the basis of this report. In 5 cases the aponeurosis of the rectus muscle was used, in 2 cases the fascia lata of the thigh was employed, while the eighth case was subjected to the use of both at different intervals of time. The technique and results of these anteropubic fascial slings which compress the bulbous urethra have been presented before the Mid-Atlantic Section of the American Urological Association in 1955 and 1956.[1, 2] The results are not completely satisfactory.

The incontinent patient as a rule is an unhappy, emotionally unstable individual. He is more than willing to undergo any type of operation which will restore his urinary continence. He should be apprised of the questionable results of all operations for urinary incontinence. A sufficient interval of time must be allowed to pass to corroborate the fact that incontinence is to be permanent and irrevocable. All pertinent studies must first be pursued and corrective surgery performed for any pathologic deviations found within the bladder and urethra which may have a causal relationship to the incontinent status.

The medical literature is replete with numerous surgical and non-surgical techniques for correction of this distressing condition. The principle of the fascial sling is not new and novel. It has been tried in the past in both male and female with indifferent results. Incontinence of neurologic origin will not be considered. The sling operation, until additional study and results are reported, should be reserved for incontinence which follows operations on the obstructive prostate, or the incontinence which follows trauma to the urethra.

It is difficult to collect a series of cases as incontinence is not commonly encountered. Of the 8 cases reported from our clinic we were directly responsible for incontinence in 1 patient 80 years of age. The remaining 7 patients were initially operated upon by others and were referred for corrective surgery.

MATERIAL

Eight patients were operated upon between 1945 and 1956 and ranged in age from 23 to 80 years. The precipitating cause of incontinence in 5 cases was transurethral prostatic resection, in 1 case perineal prostatectomy, in 1 case suprapubic prostatectomy. Trauma to the urethra with multiple operations for

[1] Uhle, C. A. W.: The fascial sling. An old surgical principle with a new concept in the correction of incontinence of urine in the male. Presidential address, meeting Mid-Atlantic Sec., A. U. A. April 15, 1955. To be published.

[2] Uhle, C. A. W. and Bradley, R. H. Jr.: The use of fascia lata strips in the sling operation for urinary incontinence in the male. Meeting Mid-Atlantic Sec. A. U. A. April 20, 1956. To be published.

TABLE 1

Case	Age	Cause of Incontinence and Diagnosis	Sling Operation	Result
1	51	Perineal prostatectomy Benign prostate	Rectus fascia 1945	Partially satisfactory
2	67	Transurethral resection Carcinoma of prostate	Rectus fascia 1946	Partially satisfactory
3	23	Urethral trauma Multiple operations	Rectus fascia 1948	Partially satisfactory
4	65	Transurethral resection Benign prostate	Rectus fascia 1950	None
5	52	Transurethral resection Benign prostate	Rectus fascia 1951	None
6	80	Suprapubic prostatectomy Benign prostate with abscess	Fascia lata 1952	None
7	62	Transurethral resection Carcinoma of prostate	1. Rectus fascia 1955 2. Fascia lata 1956	None Poor but partially satisfactory
8	28	Transurethral resection Median bar	Fascia lata 1955	None

correction and over-dilation with sounds were responsible for incontinence in 1 case, the youngest of the group. The strips forming the sling were obtained from the rectus fascia in 6 cases. Fascia lata strips were used in 3 cases in one of which rectus strips had been utilized unsuccessfully in an initial attempt to control incontinence. The ages of the patients, causes of incontinence and diagnosis, type of sling operation and dates, and results are outlined in table 1.

PHYSIOLOGIC CONCEPTS AND CRITIQUE

It was thought that the creation of an artificial sphincter about the bulbous urethra would aid in the control of urine in several ways. 1) Tension of the abdominal wall would compress the sling against the bulbous urethra. The sling would be particularly efficient in the erect posture of the patient or when intra-abdominal pressure was increased by coughing or sneezing. 2) The perineal body containing the external sphincter mechanism would be elevated and strengthened. Of interest in this respect is the recent observation of Beneventi and Marshall.[3] "The external sphincter of continent men moved upwards and downwards for a surprisingly great distance (one inch, more or less) while the subject voluntarily started and stopped the stream." 3) Urinary flow would be decreased by compression of the bulbous area of the urethra against the urogenital diaphragm. This would be comparable to the hinderance of the flow of water through a rubber hose which has been acutely angulated. A similar effect can be obtained during the act of micturition if one pulls the suspensory ligament of the penis upwards. The overall poor results in the cases reported may pos-

[3] Beneventi, F. A. and Marshall, V. F.: Studies of urinary incontinence in men. J. Urol., **75:** 273–284, 1956.

sibly be explained by the fact that these postulates have not been reproduced with the anteropubic course of the sling. The sling may lack resilience, the anteropubic course may provide the wrong fulcrum, the connective tissue about the bulbous urethra may give and permit loosening of the sling, the perineal body may not be elevated.

Lewis[4] has stated that urine is not normally held at the bulb of the urethra nor at the external sphincter but is held at the neck of the bladder. His opinion is that it is more logical to direct the surgical approach to the neck of the bladder, and to use the same principle as in the Marshall-Marchetti operation for incontinence in women. He has used this procedure twice in men after removal of all the prostatic tissue to allow angulation of the thinned tube at the vesical orifice. He had complete success in one case, failure in the second. Lewis[4] has remarked that the principle of a sling of fascia activated by striated musculature is completely erroneous. No tendon sheath or pathway for free movement of the sling is provided and any muscle pull on the sling is nullified by scarring within a few days after surgery. The sole action of the sling is elevation and kinking of the urethra.

Strong and Van Buskirk[5] have described a satisfactory result in 1 case in which a rectus fascial sling was placed retropubically at the apex of the prostate through a perineal exposure.

THREE IMPORTANT CONSIDERATIONS IN OPERATIVE TECHNIQUE

The operative technique of the fascial sling employing both the rectus fascia and fascia lata has been stressed in previous presentations.[1, 2] In the most recent edition[6] of Dodson's UROLOGICAL SURGERY a section is devoted to the fascial sling.

Attention should be directed to certain details of comparison between the rectus fascial sling and the fascia lata sling. The rectus fascial sling (fig. 1) is a time-consuming operation and large defects are left in the aponeurosis of the rectus abdominis. These should be closed with wire to prevent subsequent weakening. In excising a 1 cm. strip of rectus fascia care should be exercised in not being too near the lateral margin of the rectus muscle where perforations of small branches of the tenth to twelfth intercostal nerves are found. The strip is materially weakened if these are included, and will break when tension is applied. This unfortunate accident occurred in two patients (cases 4 and 7). In contrast the fascia lata strip is easily and rapidly removed from the lateral aspect of the thigh, is very strong and does not break with tension (fig. 2). It can be speedily placed in position.

When tunnels have been formed by blunt dissection on either side of the root of the penile body in front of the symphysis, a sufficient thickness of fibroareolar tissue must be left attached over the bulb of the urethra (fig. 3). When this bridge of perineal tissue is perforated to receive the fascial strips it should be of such strength and thickness that the sling will not be pulled distally and become

[4] Lewis, L. G.: Discussion of Uhle paper.[2]

[5] Strong, G. H. and Van Buskirk, K. E.: An operation for the cure of total urinary incontinence in the male. Report of one case. J. Urol., **66**: 234–237, 1951.

[6] Dodson, A. I.: Urological Surgery. St. Louis: C. V. Mosby Co., 1956.

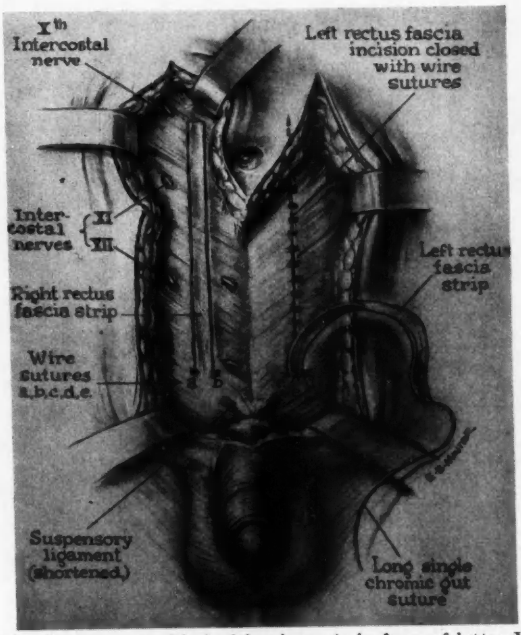

FIG. 1. Straight single suprapubic incision is made in form of letter Y. Preparation of rectus fascial strip. Rectus aponeurosis closed with wire. Suspensory ligament of penis has been shortened.

FIG. 2. Fascia lata sling attached to aponeurosis of rectus. Fascial strip should be 11 to 12 inches in length and ¾ to 1 inch in breadth. Combined perineal incision may be used to anchor it in place.

FIG. 3

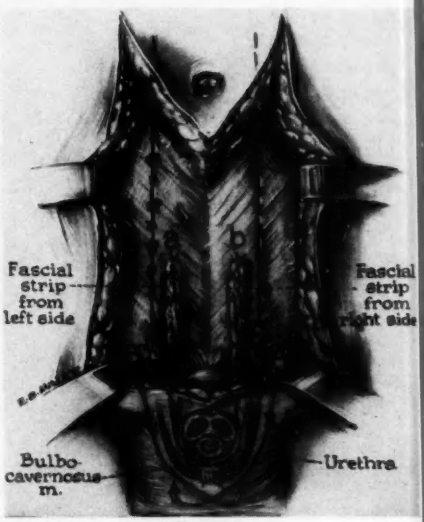

FIG. 4

FIG. 3. Introduction of fascial strips through bulbous area septum. Before withdrawing clamp from septum, ligature attached to strip (right side) is introduced into jaws of clamp.

FIG. 4. Rectus fascial sling completed and strips sutured to rectus aponeurosis. Amount of tension to be placed on these strips is dependent upon absence of urethral flow when assistant makes pressure upon previously filled bladder.

ineffective when tension is placed on it (fig. 4). The fascial strip may be secured in position through a combined perineal incision.

The amount of tension or pull to apply to either type of sling can be grossly measured and is a most important part of the overall technique. The bladder is filled to capacity with sterile water. Pressure upon the bladder is made by an assistant. Tension is made on the sling, and when water no longer can be forced through the urethra, the fascial strips are anchored in place by wire sutures.

COMPLICATIONS

No serious postoperative complications have resulted in the group of 8 patients.

In only one patient (case 1) a urinary fistula developed, which drained through the lower portion of the suprapubic incision. It closed rapidly with catheter drainage.

In a second patient (case 2) an indwelling urethral catheter was not employed postoperatively. This error in judgment was followed by retention of urine. In attempting to pass a catheter, the urethra was perforated. In order to restore continuity the entire sling component was freed and then restored. Following adequate catheter drainage no fistula developed.

There have been no cases of urethral necrosis and sloughing with extravasa-

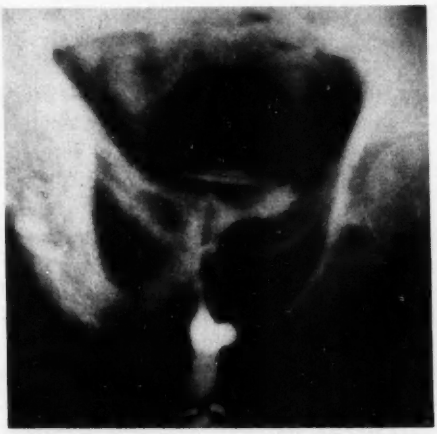

FIG. 5. Case 2. Dilation of urethra proximal to sling. Anteroposterior view.

tion. Cooney and Horton[7] reported one such complication twenty-four hours after removal of the indwelling catheter. Campbell[8] has informed me that urethral sloughing occurred 1 year after a successful functional result in one of his cases.

Pain in the groins, perineum and penis has not been a constant, long lasting complaint. In some cases it has been severe in the immediate postoperative period and required much sedation. Persistent cystitis, urethritis, edema of the penis and scrotum have been infrequent concomitants and of temporary duration.

The most serious delayed complication is the development of a diverticulum in the urethra proximal to the sling. In two of 3 patients (cases 1, 2, 3) with the most satisfactory results in the series of eight, outpouching and dilation of the urethra occurred (fig. 5, case 2). Two patients referred to Lewis,[4] after failure of the sling operation, had diverticula. In both these cases, the urethra was markedly dilated from the point of the obstructive sling to the bladder. In spite of the damage to the urethra by obstruction they were totally incontinent. If this complication should be a rather common finding in cases reported in the future the operation should be discontinued.

RESULTS

The sling operation has been partially effective in 50 per cent of cases (cases 1, 2, 3, 7). These patients could stop and start the urinary stream at will, in the erect posture and void a variable quantity of ounces. However, as soon as there was any stress or the patient did not have his mind on control, dribbling occurred. Three of these patients (cases 1, 2 and 3) rated their dribbling as of minor consequence compared to their preoperative status. Two patients (cases

[7] Cooney, C. J. and Horton, G. R.: An operation for the cure of urinary incontinence in the male. J. Urol., **66**: 586–592, 1951.

[8] Campbell, E. W.: Personal communication.

1 and 3) had the sling shortened or reefed with beneficial but imperfect results while shortening of the sling in one patient (case 8) was valueless.

Cooney and Horton[7] have reported good control in two of three patients. Scott,[9] in his editorial notation in the YEARBOOK OF UROLOGY (1952) stated that he and his associates had performed the sling operation on 4 patients. Control was judged good in two and considerably improved in two. Lewis[4] operated upon one patient with no result. Campbell[8] has reported good control in three patients after use of this procedure.

According to Dodson,[6] Millin has employed the fascia lata sling placed anterior to the pubis with satisfactory results.

In analyzing the results, individual or a combination of factors can be invoked to explain the overall poor results. Technical reasons for failure would include operative errors in preparing the strips of fascia. The strips may be too short for proper adjustment on the abdominal fascia, or they may tear during preparation. It is difficult to improvise if this happens. Failure is the end result. An indwelling catheter should always be inserted at the conclusion of the operation. An obvious cause of failure is insufficient tension of the sling upon the urethral component. An explanation may be, that as time passes in the immediate postoperative period, the sling advances distal to the original site of adjustment because the fibrofatty areolar tissue, forming the septum over the bulbous end of the urethra, is not strong enough to maintain the sling in permanent position.

SUMMARY

Eight patients were operated upon for incontinence of urine in whom a periurethral fascial sling coursing anterior to the symphysis pubis compressed and angulated the urethra. Strips of fascia to form the sling were obtained from rectus aponeurosis and fascia lata of the thigh. Results were partially effective in fifty per cent of cases. A critique of the physiologic concept of the procedure, the comparative evaluations in the technique of the operation with its complications and the author's reasoning for failure of the operation have been presented.

CONCLUSION

The validity and usefulness of a surgical technique for the correction of incontinence of urine depends upon the maintenance of principles of physiologic integrity. The fascial sling as discussed in this paper is not basically physiologic. It is the author's opinion that an additional period of study and analysis of cases on the part of numerous observers are indicated.

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[9] Scott, W. W.: Editor's Insert. Year Book of Urol. Chicago: Year Book Publishers 1952, p. 251.

DISCUSSION

DR. VINCENT J. O'CONOR (Chicago, Ill.): Dr. Uhle and Dr. Cooney and others have restimulated our interest in trying to effect some sort of a mechanical improvement in these male patients with urinary incontinence which has followed some sort of operative procedure on the bladder neck.

We used the procedure which Dr. Uhle, I think, originally suggested. I wasn't familiar with it, unfortunately, until after Dr. Cooney presented it at the North Central Section. We used this procedure in 2 cases. It's not a simple procedure, and its morbidity is somewhat prolonged, but if it could effect what we want it to, it certainly would be worth while.

There's so much we don't know about incontinence of urine in the male and the female that, when we talk about physiological factors, it's a little like discussing essential hematuria. While the male mechanism is more clearly understood than that of the female, there are still a lot of factors we should know much more about.

Presumably continence is improved by offering some sort of resistance to the overflow of urine, mechanical resistance. Certainly we have been in the last few years very much interested in continence of urine in women. Up to that time, we passed them along to the gynecologists, and they didn't cure them in many instances; the patients returned to us, and we have been operating on more and more women with urinary stress incontinence, either partial or complete, and we have been gratified at the good results we have been effecting.

We have done about twenty Marshall-Marchetti procedures now, and I'm amazed at the excellent results we have obtained in patients who have been operated upon a number of times by experienced surgeons without any improvement.

In using Dr. Uhle's procedure, we had about a 50 per cent improvement in the first patient. He was a man who had had a suprapubic prostatectomy done, as somebody said, in the great hospital elsewhere; we were rather pleased, and so was he, although he was in the hospital for 3 weeks.

The next patient we did this procedure on got little or no improvement.

I was discussing this matter with Terence Millin and he said, "Why don't you simply take a strip of fascia and buttonhole the external inguinal canal region and the perineum, and pull it through and put it under tension in that way?"

So, since that time, we have done twelve of these rather simple procedures. It's not an extensive procedure because what we do is, have one man make an incision in the perineum, and simply develop the perineal spaces without cutting the central tendon. It may act as a bridge against having the sling slip forward; and then with one of us on either side, we make a 2-inch incision over the inguinal ring on either side, and the man working on the perineum pushes it back until he can get it as far back of the triangular ligament as possible. We have been using black silk to fasten the sling to the conjoined tendon on either side.

We use bovine fascia lata strips, which we were able to procure from Bauer

and Black, and we found that these did not slough out; that they worked quite well; for a while they quit making bovine fascia lata, so we had to go to getting our own strips from the fascia lata of the same patient.

Taking the strip from the thigh is a much more formidable procedure than putting in the sling of bovine fascia.

Then we thought we'd try using broad ribbon gut, so we got some broad ribbon gut made, about an inch wide, and we found that that acted as a foreign body; that instead of being surrounded by fibrous tissue, it sloughed out.

Then I got the wild idea of using a strip of tantalum wire, and that was the worst idea I had, because it caused a lot of tissue irritation and had to be removed operatively.

Now, the bovine fascia lata is now again available, and, in our experience, it's just as good, if not better than the fascia lata of the patient.

As Dr. Uhle said, all of these sling procedures are discouraging. If you get a 50 per cent improvement in these patients, the patients are quite happy, especially if you have emphasized to them before the operation that the chances of getting any improvement at all are questionable. In other words, this is one procedure where you cannot promise the patient a definite result.

We have had a man that Dr. Irwin sent down from Milwaukee upon whom he had done a suprapubic prostatectomy; a big, fat man, a brewer. Most of these people have a lot of fat on their abdomens and a lot of increased peritoneal pressure. In fact, I have seen only one of them with a partial stress incontinence who was really thin, so I think their general build has something to do with its development, as well as the trauma of the procedure.

But this chap, we did first of all a fascia lata—his own fascia lata—operation on him. He was a bachelor and a man in his middle seventies, and he got very little improvement. We could not get him out of the hospital. He wanted to stay around, and finally we got him back to Milwaukee, and Dr. Irwin said, "You have got to operate upon this fellow again, because he's wetting the floor, and he doesn't like to wear a clamp or a bag."

I said, "I'm sure we won't get any improvement," but he came down and we then used a bovine fascia lata strip which we pulled up very tightly. Dr. Bulkley usually works through the perineum; Dr. Sokol is on one side and I'm on the other, and the great thing is to know how much tension to put on it. Dr. Millin says the way to find that out is to put 300 cc water in the bladder, pull up on the sling until it is tight enough so that you cannot get the urine out of the bladder by credé-ing the suprapubic region.

This German brewer got a satisfactory result after the second procedure. He's now continent and happy.

We had another man who was quite an athlete—in his early eighties—who loved to go in the surf, and he was very much disturbed because he wet himself when he was running around the beach and swimming, and he had a large left inguinal hernia. We did a bovine fascia lata sling on him with 30 per cent improvement. He came back a year later and we referred him to a surgeon for repair of a large left inguinal hernia. After his hernia was repaired, he had complete control of urine. Whatever mechanical or anatomical factors were involved

in the control of the hernia, apparently were sufficient to bring about enough resistance along with a pull on the sling to cure his stress incontinence.

This is an important subject because it represents one of the few aspects of surgical urology in which we have not been able to make real progress. We are very much indebted to men like Dr. Uhle and Dr. Cooney and Terence Millin for their ingenious suggestions as to sling therapy.

If we could only devise some sort of procedure which would be similar to the Marshall-Marchetti operation, it might work in the male, although I think our anatomical and physiological problems may be quite different in the male than in the female.

DR. EDWARD W. CAMPBELL (Philadelphia, Pa.): May I ask Dr. Lattimer a question? Do you find a suprapubic tube for total drainage is adequate to keep your patients dry? We have been unable to keep our patients from draining urine through the urethra even with sump drainage. In all cases urine has passed through the urethra and broken down tissue so our operation has been ruined.

DR. MEREDITH F. CAMPBELL (Miami, Fla.): I have a question for Dr. Lattimer. On the assumption that the child normally acquires normal urination at the age of 30 months, I would be interested to know how many of his patients past thirty months are continent.

DR. FRANK HINMAN, JR. (San Francisco, Calif.): I have a question, indirectly, for Dr. Lattimer. I am a skeptic and would like to know how many men with total incontinence, with epispadias, operated on at the external sphincter gained continence?

DR. HARRY M. SPENCE (Dallas, Texas): I would like to say just a word in defense of my position of putting the ureters into the bowel. While not primarily my topic, I would like to comment that the problem of continence is a matter of definition. It's like Dr. Heckel remarked the other day: How high is up?

I contend that the normal infant is continent from the time he is born in the sense that he has a competent sphincter. Certainly infants don't dribble all the time. So, I fear that the hope that true continence will be established with the passage of time after the infolding procedures, may be overly optimistic.

Next, I believe that the principle of turning the bladder in is described as simply the principle of causing an obstruction to the outflow of urine, and was done many times many years ago by master surgeons, and they didn't get away with it. I think we are now getting away with it technically because, as John Lattimer mentioned, we have antibiotics and that sort of thing.

So, while I think that his efforts and the efforts of others along the same lines are most commendable, I must await further long-term experience with the method, especially with regard to the control of urination before I shall discard ureter to bowel transplant despite the admitted advantages of the latter.

I think we are dealing with damaged goods to start with in the exstrophy problem, and I do not think we can expect a perfect result. I do not want to be put down as unduly conservative or sticking to my guns in the face of better evidence, but I just have not seen the better evidence yet in the sense that the results of bladder reconstruction are superior to ureterosigmoidostomy in this condition.

Dr. John K. Lattimer (New York, N. Y.): In reply to Dr. Edward W. Campbell's question about difficulty with cystotomy drainage, in these cases let me say that even though there was leakage of urine around the tube in some cases, we haven't had a breakdown as yet.

I do think that a suprapubic tube is safest. I would not attempt to get away with a urethral catheter.

In regard to Dr. Hinman's question about patients with epispadias, and whether they achieved continence after operation, let me say that part of our hope is based on the fact that we have seen occasional men with very short, epispadiac urethras, who have, by voluntary educational maneuvers, apparently strengthened their perineal musculature to the point where they had some control. We hope that some of these children, who never knew anything about making an effort at continence previously, may be able to build up their muscles, just like an incontinent woman can do, in attempting to achieve control.

If the urethra is made too snug at the time of operation, one may achieve a stricture which will cause reflux, as happened in some of our children. This damaged the kidneys. It is my understanding that one of the cases that Dr. Young did a few years ago was found ultimately to have so much of a stricture that a suprapubic tube was needed.

In regard to Dr. Meredith Campbell's question, at 30 months, none of our children who have undergone this operation are continent; all of them are behind their own age group in this respect. One must remember, however, that a normal child of this age has had a urethra with which to practice, for many more months than these children. We must allow them time to learn how to use a urethra.

I certainly think that the continence question is the real crux of the matter, and if by following these children longer we find they are not continent, the operation as we have been doing it, must be regarded as unsuccessful.

Now, Dr. Sam Vest has asked me to show 2 cases of his. He has done 2 cases in older children; children of six or seven years of age. In both cases he has achieved continence, and the families are delighted.

One of them is very satisfactory. The second one is not satisfactory because the child continues to have fever, and he attributes this to the fact that the child has reflux up the ureters. Dr. Vest states that the urethra accommodates a 16F catheter very easily. The child has satisfactory control with the ability to hold the urine for three or four hours at a time.

Dr. Vest is worried by the fever to the extent that he is thinking of taking this down and converting it to one of his usual type, transplanting these ureters into the rectum and doing a colostomy above, but there is no question about urinary control in his mind. He thinks that this is not a problem, and the result has been satisfactory from this standpoint. Dr. Vest does a little variation, by splitting the trigone and sinking the urethra a little farther down into the base of the bladder.

Dr. Charles A. W. Uhle (Philadelphia, Pa.): I appreciate Dr. O'Conor's remarks. The use of bovine fascia lata would materially improve the technique of operation, by decreasing the time element. It's not too difficult to take fascia lata from the thigh, but it just adds to the procedure.

As far as setting the sling is concerned, I originally placed a catheter in the

urethra and then pulled up on the sling before fastening the strips to the rectus fascia. Now I remove the catheter after filling the bladder with water. When you can't force water with suprapubic pressure through the urethra, that the "N" point of the tension. The sling is set at this point. An indwelling catheter is inserted at the conclusion of the operation.

May I have the privilege of showing seven kodachromes of the fascia lata technique?

PRESIDENT HECKEL: Certainly.

DR. UHLE: We'll go through them rapidly. They are self-explanatory.

(Slide) We can see the appearance of the fascia lata when it is spread out. These strips should be 11 or 12 inches long.

(Slide) This is the suprapubic incision made over the right rectus muscle. The rectus fascia is exposed.

(Slide) This will show you the simplicity of the technique. After the suprapubic incision is completed by blunt dissection a tunnel is made alongside the penile body. This is a rubber dam for delineation and retraction purposes emerging from a perineal incision. You can almost see the texture of the fascia lata as it lies in its course. It is important to preserve the periurethral tissue about the bulb of the urethra, as emphasized in the paper.

(Slide) This depicts the fascia lata on the right and left side of the bulb.

(Slide) A closer view, showing the fascial strips before they are attached to the rectus fascia. As I recall, Dr. Q'Conor said he fastened the strips to the conjoined tendon.

(Slide) This slide demonstrates the suprapubic pressure tension test. An assistant makes pressure on the previously filled bladder. Tension is placed on the sling. When water cannot be forced through the urethra the strips are fastened to the rectus fascia with wire sutures.

(Slide) The final kodachrome shows the strips after they have been sutured to the rectus fascia.

DR. O'CONOR: Did I understand that you do not use an indwelling catheter after completing the operation, Charlie?

DR. UHLE: Yes, by all means. An indwelling catheter is most important.

PRESIDENT HECKEL: I don't think, Frank, they have answered your question. Is that true or false?

DR. HINMAN: I don't think they have.

PRESIDENT HECKEL: Well, as a parliamentarian, I would say, will you restate your question?

DR. HINMAN: I'd like a show of hands of the number who have had a patient with epispadias—and generally they are incontinent—who have successfully obtained continence after operation.

PRESIDENT HECKEL: Raise your right hand.

DR. J. HARTWELL HARRISON (Boston, Mass.): I know of one case, but I have never achieved it.

(Eight members held up their hands.)

DR. HINMAN: The reason I ask is that, although epispadias is less common than exstrophy, if we can't obtain continence in those cases after all these years, how can we expect to do it with exstrophy?

URETERAL SUBSTITUTION BY ISOLATED ILEAL LOOP: ILEOURETEROPLASTY AND ILEOPYELOPLASTY

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Clinical experience with the grafting of isolated small bowel segments to the urinary tract is still limited. There has been a long delay in accepting such procedures which were first suggested in 1888. In that year Tizzoni and Foggi[1] replaced the bladder in a dog with an isolated small bowel loop anastomosed to the proximal urethra. A few years later in 1894 Fenger[2] discussed the possibility of replacement of the ureter with small intestine; apparently he never executed his suggestion. A very long delay occurred before Fenger's idea of replacing the ureter was applied clinically. Bitker[3] in reviewing the literature on this subject found only 3 clinical reports of ileoureteroplasty prior to 1950, and a total of 17 until 1953. Since then various authors[4-9] have published 19 additional cases, bringing the present total number to 36. Two additional cases are embodied in this report. In one of them an ileopyeloplasty was done. Such an operation is reported in only four of the previously published cases.

The histories of the 2 patients reported here are given in some detail, because they illustrate so clearly the dangers of prolonged ureteral catheter drainage. Likewise, the operative reports are detailed because of the lack of precise information of the technique employed in most of the published reports.

CASE REPORTS

Case 1. Ileoureteroplasty. A.M., aged 48, was first seen in 1947, when cystoscopy revealed a flat, solitary tumor involving the posterior wall and fundus of the bladder. A partial cystectomy was done. Eight months later two small lesions were excised transurethrally from the floor of the bladder neck, an area remote from the original growth.

Unfortunately no further examination was possible until 7 years later when in 1954 the patient re-appeared with a large flat tumor involving the entire upper half of the internal orifice of the bladder and the adjacent superior wall

[1] Tizzoni, G. and Foggi, E.: Die wiederherstellung der Harnblase. Centralbl. f. Chir., **15:** 921, 1888. (See Melnikoff, A. E.: Sur le remplacement de l'urètere par une anse isolee de l'intestin grêle. Rev. Clin. Urol., **1:** 601, 1918.)

[2] Fenger, C.: Operation for relief of valve formation and stricture of ureter in hydro- or pyonephrosis. J. A. M. A., **22:** 335, 1894.

[3] Bitker, M. P.: Les urétéro-iléo-plasties. J. d'urol., **60:** 473, 1954.

[4] Baum, W. C.: Clinical use of terminal ileum as a substitute ureter. J. Urol., **72:** 16, 1954.

[5] Moore, E. V., Weber, R., Woodward, E. R., Moore, J. G. and Goodwin, W. E.: Isolated ileal loop for ureteral repair. Surg., Gynec. & Obst., **102:** 87, 1956.

[6] Rack, F. J. and Simeone, F. A.: Uretero-ileal and pyelo-ileal neocystostomy in man. Ann. Surg., **140:** 615, 1954.

[7] Ortved, W. E.: The use of a segment of ileum to replace a portion of ureter. Canad. Med. Assoc. J., **71:** 12, 1954.

[8] Pyrah, L. N. and Raper, F. P.: Some uses of an isolated loop of ileum in genitourinary surgery. Brit. J. Surg., **42:** 22, 1955.

[9] Foret, J. and Heusghem, C.: Replacement of both ureters by an ileal graft. Lancet, **1:** 1181, 1953.

in the so-called blind area. Cystoscopically this tumor appeared much more malignant than the original lesion. Transurethral biopsy confirmed the clinical impression of a more anaplastic tumor superficially invading the bladder well.

Total cystectomy, prostatectomy, and seminal vesiculectomy were accomplished in July 1954. The ureters were brought to the skin of the anterior abdominal wall. In the immediate postoperative period the distal portion of the left ureter sloughed, requiring excision and reimplantation in the abdominal wall. A good external rosette was obtained, and the patient was discharged from the hospital wearing a Singer cup. Since that time, 2 years ago, no further difficulty has been encountered on that side, and that kidney remains apparently normal.

On the right an adequate external nipple of ureter was not obtained, and an indwelling catheter was necessary. All the usual complications associated with this type of drainage resulted. Within 4 weeks, the first of many episodes of acute pyelonephritis occurred. For several months leakage of urine from the skin stoma about the catheter was a source of annoyance. Increasing difficulty began to be encountered in changing the catheter. Finally, 5 months after cystectomy, this became impossible. The fibrosed and stenosed distal portion of the ureter was excised, and a new cutaneous ureterostomy was made in December 1954. Continued use of a catheter was necessary, and the patient was almost constantly disabled by pain and pyelonephritis.

Repeated x-rays showed increasing pyelonephritic destruction of the right kidney (fig. 1, *A*) and 8 months after cystectomy the urinary output from the kidney began to decrease. Finally, 15 months after the bladder excision in October 1955, operative interference seemed imperative in order to preserve the remaining renal function. At that time, even though the left kidney was normal, it was not thought advisable to remove the damaged right kidney. It seemed obvious that what was required was a new ureter which would not require an indwelling catheter.

Operation (October 25, 1955): A long right paramedian incision was made. The small bowel was displaced into the left side of the abdominal cavity. An incision was made longitudinally through the peritoneum overlying the ureter which could be felt as a laterally placed tight band, extending from the posterior abdomen to the anterior abdominal wall. This peritoneal incision deviated superiorly and inferiorly, lateral to, and parallel with the cecum and ascending colon. Inferiorly it extended to the cecal tip, superiorly to the upper margin of the transverse colon. The cecum, ascending colon, and hepatic flexure were reflected medially without difficulty. The ureter was then dissected free from the posterior abdominal wall. The distal portion was densely fibrosed and grossly thickened. This change extended almost to the lower pole of the kidney where the ureter became relatively normal and easily intubated. Immediately below this area a definite stricture could be identified.

The kidney itself was high and tightly embedded in fibrous tissue. It could not be well defined by palpation. It was thought that if an anastomosis to the renal pelvis were necessary, this anterior approach would not be satisfactory or

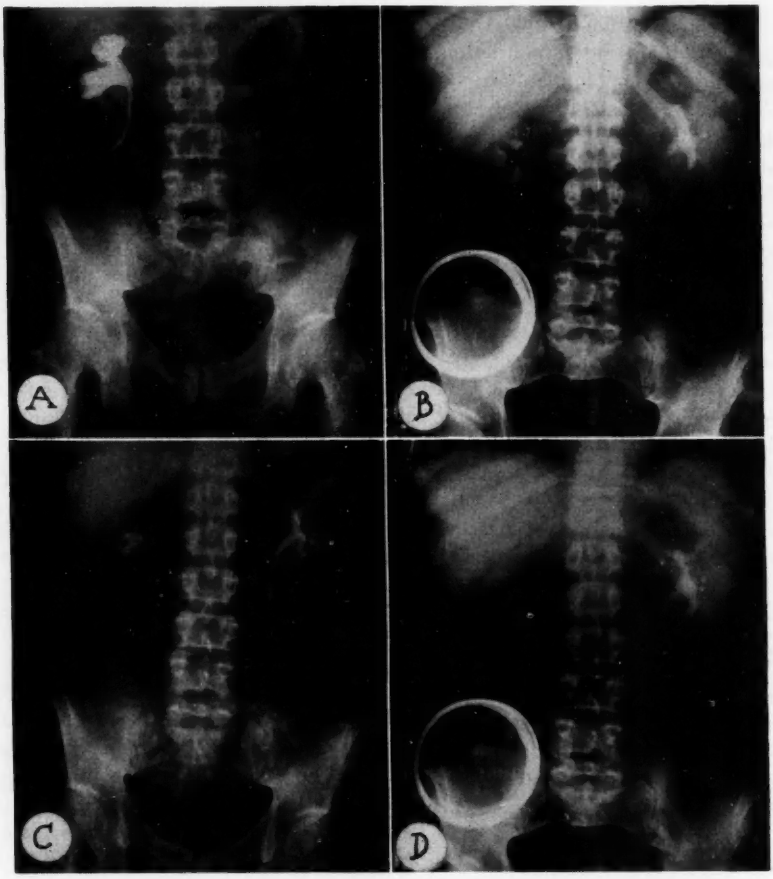

FIG. 1. Case 1. *A*, retrograde right pyelogram. Extensive pyelonephritic damage after 7 months of catheter drainage. Further destruction occurred prior to ileoureteroplasty, 8 months later. *B*, 2 weeks after ileoureteroplasty. Excellent function (5-minute film); calyceal pattern already returning to more normal appearance. *C*, 8 weeks after ileoureteroplasty. Note relatively normal left upper urinary tract after 20 months of successful "cup" drainage. *D*, note remarkable improvement in right kidney 8 weeks after ileoureteroplasty (15-minute film).

adequate. The accuracy of this observation was proven by the findings in our second patient.

Inspection of the ureter showed that division at about the lower pole of the kidney would be satisfactory (fig. 2, *A*). Attention was then directed to the formation of a small bowel loop. The ileum was divided 6 inches from the ileocecal valve and again 12 inches proximal to that point. In order to obtain adequate mobilization it was necessary to divide the mesentery almost to its base at both ends of the loop. Great care must be exercised in this portion of the

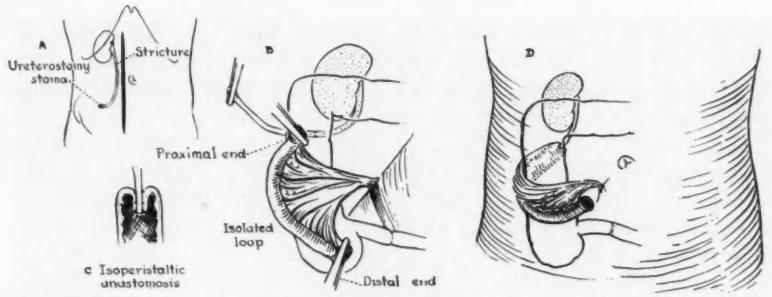

FIG. 2. Case 1. *A*, loop brought anterior to both large and small bowel. Ureter later severed just below transverse colon. *B*, anastomosis completed. Relationship of colon, loop and ureteral stump.

dissection lest a major vessel of supply to the required loop be divided inadvertently. This is best prevented by first carefully inspecting the vascular pattern, and then dividing separately, over the opened blades of a blunt instrument, the two peritoneal layers enclosing the vessels and fat of the mesentery. As the mesenteric division proceeds, the proximal end of the loop can be brought repeatedly, if necessary, to the anastomotic site to determine whether sufficient mobility has been obtained. When the loop was sufficiently mobilized, an end-to-end anastomosis of the ileum was done beneath the ileal loop (fig. 2, *B*). The mesenteric defect was then closed with interrupted sutures. The loop with its attached vascular pedicle then lay on top of the reformed mesentery.

The best fit with the ureteral stump seemed to be achieved by bringing the loop around the lateral aspect of the hepatic flexure to the ureter. The apposition thus obtained appeared to be more satisfactory than that which would have resulted from the insertion of the loop through the mesentery of the flexure. When the course of the new channel had thus been determined, the dilated proximal ureter was divided obliquely and anastomosed directly to the proximal end of the ileal loop behind the hepatic flexure. Interrupted through and through sutures were used as a first layer inverting both ureteral and bowel walls. A mucosal-to-mucosal junction was thereby effected. Two additional layers of interrupted sutures were placed through the bowel serosa and adventitia of ureter. These two layers of sutures inverted the end of the loop with its attached ureter. An internal nipple of the ureter with the attached inverted bowel wall was thus produced. The ileal loop was brought around the lateral side of the ascending colon, thence along its anterior surface. Internal herniation was prevented by suturing the loop and its mesentery to the underlying large bowel and adjacent peritoneum (fig. 2, *C*, *D*).

The colon was then secured in its normal position by approximating the divided margins of the posterior peritoneum.

The distal end of the loop was brought forward directly to the abdominal wall, and a cruciate incision was made in the fascia to diminish the possibility of future stenosis. Several stitches approximated the bowel serosa and peritoneum. Finally the protruding nipple of bowel was everted and stitched to the skin.

Postoperatively, no difficulties were encountered. A Foley catheter was left in the loop for 4 days, after which a Singer cup was cemented over the stoma.

The preoperative lumbar pain was relieved completely, and the patient's toxicity disappeared. His general condition rapidly improved in every way. Most pleasing was the rather startling improvement in the functional capacity and pyelographic appearance of the right kidney (fig. 1, *B*, *C*, *D*). At this time, 8 months after his operation, he seems to be completely rehabilitated.

Case 2. Ileopyeloplasty. Mr. R. M. was seen at the age of 44 because of symptoms suggesting bladder infection. The bladder mucosa was found to be thickened and coarsely edematous in an extensive area involving the trigone and the entire bladder neck. The cystoscopic appearance suggested an inflammatory lesion and biopsy was negative for tumor. Treatment of the existing infection produced no relief.

Nine months later a second cystoscopy revealed mucosal changes of the same type, but more severe in character. Biopsy revealed a transitional cell epithelial carcinoma with superficial invasion.

Intracavity radiation was administered from a central radium source. The calculated administered surface dose at the bladder outlet was 5,800 r, with 4,400 r at a depth of 3 cm. The dose to the bladder vault was calculated at 5,000 r in an overall time of 5 days.

Five months later the bladder capacity was 375 cc. On this occasion cystoscopy revealed a marked improvement in the appearance of the mucosa in the trigonal region. Again no actual tumor mass could be seen anywhere in the bladder. In large areas, however, the previous changes were observed. Both sides of the bladder neck and the entire right bladder wall were involved in a coarsely edematous, granular change, characteristic of infiltrating neoplasm. Biopsy of these areas revealed tumor of the type previously observed.

Because of the diffuse nature of the cancer and the widespread instability of the bladder mucosa, a total cystectomy seemed advisable. This was accomplished October 14, 1953, one year after the original cystoscopy. The bladder, prostate, seminal vesicles, and all pelvic lymph tissue were excised. The ureters were transplanted to the skin. The excised specimen showed only superficial invasion of the bladder wall and intramural lymphatics. The obturator and all pelvic lymph nodes were negative for tumor.

Many attempts were made to utilize Singer cups, but inevitably leaks developed, and unfortunately the patient was discharged wearing indwelling catheters on both sides. During the next month there was constant low grade fever with occasional exacerbations. Slight discomfort was present frequently in the left renal area.

One month after leaving the hospital, the patient was readmitted with acute left pyelonephritis, and a blocked left catheter. Reinsertion of a catheter on that side was not possible, and due to the existence of definite ureteral obstruction, exploration was necessary. The distal ureter was found to be densely fibrosed and narrowed. This terminal portion, about 3 inches in length, was excised and a new cutaneous stoma constructed.

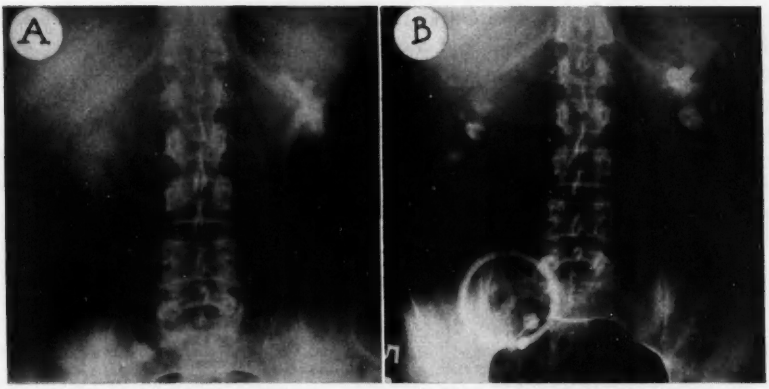

FIG. 3. Case 2. *A*, 3-hour excretory urogram showing condition of right kidney after 28 months of ureteral catheter drainage. No visible concentration of dye until 30 minutes after injection of dye. *B*, 3 months after ileopyeloplasty. Good concentration of dye (5-minute film). Marked improvement in calyceal pattern.

The ensuing year was relatively uneventful, until its very end, when bilateral pyelonephritis appeared. The infection was particularly violent on the right side. A dense mass became palpable in the renal area; it was thought that pyemic abscesses of the kidney and perinephritis had developed. A hectic fever persisted nearly 2 weeks. A mixed infection was found in both kidneys, but Pseudomonas aeruginosa was the dominant organism. After several drugs had been given without effect, polymixin eventually controlled the infection. During this illness some diminution in the function of the right kidney became apparent.

In the second post-cystectomy year two hospital admissions were necessary for pyelonephritis in the right kidney (fig. 3, *A*). On several occasions difficulty was experienced in replacing one or the other catheter. Finally at the end of the 2 years in December 1955, neither catheter could be inserted. Fortunately, there was an adequate mucosal outpouching on the left. A Singer cup was applied with greater success than previously, and has been worn since then without difficulty.

On the right side, without a catheter over a 4-week period, from December 15, 1955 to January 14, 1956, the urinary output rapidly decreased, due to stenosing ureteritis. After repeated efforts a filiform bougie was passed, and a catheter was inserted to the renal pelvis. With adequate drainage the kidney quickly regained its functional capacity.

The problems at this time seemed similar to those of the previous patient; first, the necessity for preserving the kidney; and, secondly, of providing a good functional ureter which would not require permanent intubation.

Operation (January 24, 1956): See figures 4 and 5. A midline incision was made. The small bowel was packed off in the left side of the abdomen. The thick rigid tube of ureter was readily identified coursing up to the anterior abdominal wall.

The appendix was adherent to the lateral abdominal wall, and would have interfered with mobilization of the cecum. A routine appendectomy was done.

The cecum, ascending colon, and hepatic flexure were mobilized and displaced

medially. Access to the ureter was thus obtained. It was divided just beneath the anterior abdominal wall and mobilized by sharp dissection. When several inches had been freed, catheterization was attempted. Impassable obstruction was encountered at what was thought to be the ureteropelvic junction. The ureteral dissection was carried as high as possible, but the renal hilum could not be visualized. The kidney was high and densely incorporated in a mass of scar tissue. It was decided that it would not be possible by means of an anterior approach to bring an ileal loop to the renal pelvis (fig. 4, *A*).

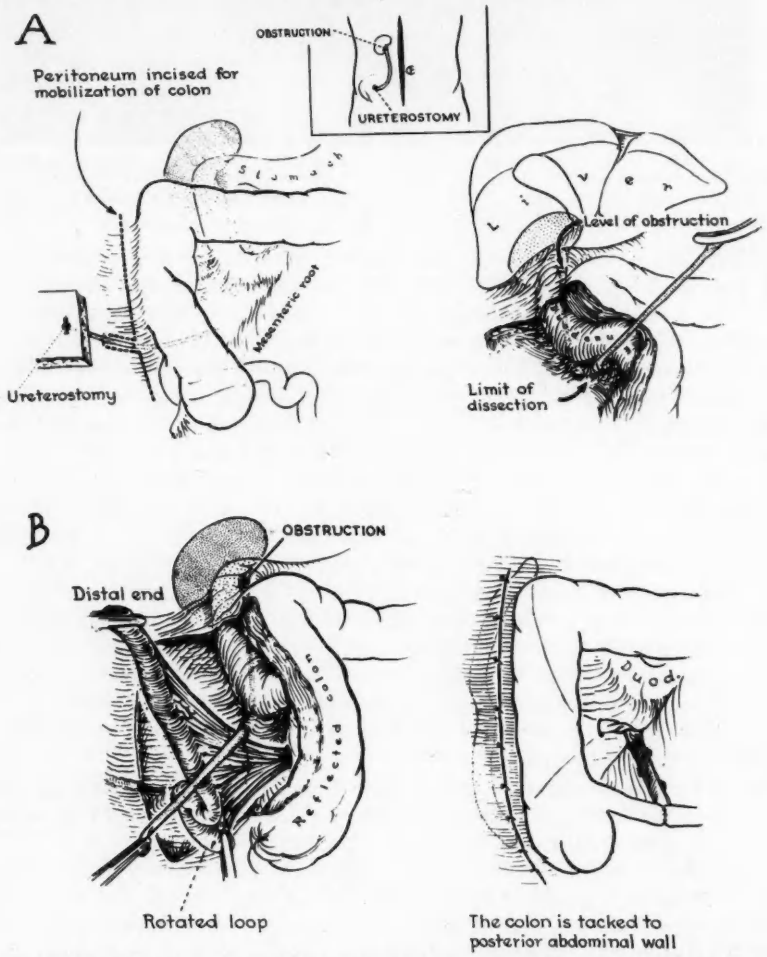

FIG. 4. Case 2. *A*, large bowel displaced and duodenum partially freed. Renal hilum still well above area of dissection. *B*, loop fully mobilized and passed through mesentery of ascending colon. Right drawing shows loop in its new retroperitoneal position.

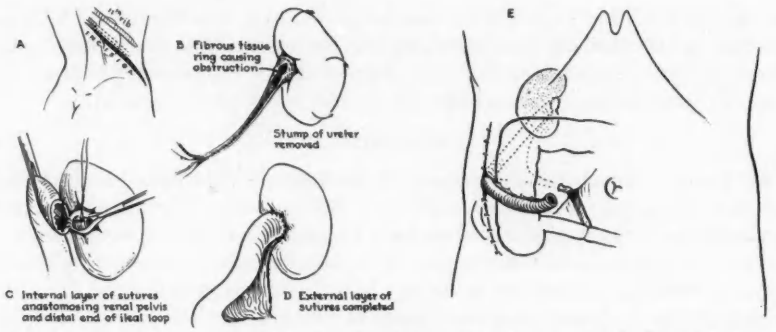
A
B Fibrous tissue ring causing obstruction
Stump of ureter removed
C Internal layer of sutures anastomosing renal pelvis and distal end of ileal loop
D External layer of sutures completed
E

FIG. 5. Case 2. *A*, posterior dissection showing method of anastomosis. *B*, antiperistaltic anastomosis completed. Proximal end of loop sutured to renal pelvis; distal end opening on skin.

A 10-inch loop of distal ileum was isolated. The loop with its intact blood supply was passed through the mesentery of the ascending colon, and placed retroperitoneally in the right abdominal gutter. At this time, one end of the loop should have been brought to its final position in the anterior abdominal wall; instead, the abdomen was closed with the entire loop beneath the posterior peritóneum (fig. 4, *B*).

The patient was then placed on his left side and the kidney exposed through the bed of the twelfth rib. The kidney was mobilized with difficulty by sharp dissection, which was necessary due to the marked fibrous perinephritis. The ureter was divided longitudinally, and almost complete occlusion was found at the hilum of the kidney, the pelvis itself being entirely intrarenal.

The posterior rim of the renal hilum was retracted and an opening 1 inch long was made in the pelvis. The ileal loop approximated this opening more easily when rotated. A No. 20 Foley 5 cc catheter was passed along the loop into the renal pelvis. Then an antiperistaltic anastomosis was made. A mucosal-to-mucosal union was effected with interrupted sutures of No. 000 chromic catgut. These were reinforced with a second external layer (fig. 5, *A*, *B*, *C*, *D*).

The posterior portion of the incision was then closed and the patient rotated to a partially supine position. The proximal portion of the ileal loop was then brought through the posterior peritoneal layer, lateral to the cecum, to the anterior abdominal wall. The manipulation of the loop within the abdominal cavity was a blind procedure and should have been done at an earlier stage (fig. 5, *E*).

The first few days after operation were associated with an expected adynamic ileus. However, adequate bowel motility did not return and there was persistent moderate painless distension. This had not been relieved by the tenth postoperative day. A superadded mechanical factor in the obstruction was suspected and the abdominal wound was reopened. Two softly adherent loops of small bowel were found in the true pelvis. They were separated by finger dissection, and an enterostomy was done above the obstructed area.

The patient's further convalescence was uneventful. In the subsequent months

his general condition has improved markedly (fig. 3, *B*). No episodes of fever, so common in the past, have occurred, and he has resumed his professional work. There seems no reason why future difficulties should be encountered. A Singer cup has been worn successfully over the ileal stoma ever since the operation.

DISCUSSION

The provision of adequate drainage and the removal of the infection-producing catheters has had a profound effect on both these patients. Their general health has improved so markedly that they have resumed their former occupations.

During the early postoperative period, for approximately three weeks, almost daily removal of the cups was necessary in order to evacuate mucus. With the passage of time its production has seemed to diminish, and at present the cups are being changed every 4 to 5 days. If they are left in place too long, calcareous debris will collect on the skin, and may give rise to dermatitis.

In only 4 of the 33 reported ileoureterostomies has the bowel loop been anastomosed to the renal pelvis. Two of these were reported by Baum,[4] one by Moore,[5] and one by Rack.[6]

In Baum's patients the left ureter was replaced. The ileal loop was passed around the lateral aspect of the colon in one patient, and through the mesocolon in the other. Access to the left renal pelvis probably is easier than to the right.

Both Moore and Rack replaced the right ureter. In Moore's patient the kidney seems to have been low, with an elongated extrarenal pelvis. The anastomosis was done at a relatively low level inferior to the hepatic flexure. Rack anastomosed an ileal loop to the pelvis of a solitary kidney. The patient had worn a nephrostomy tube 2½ years. As with our patient, who wore a ureteral catheter, recurrent attacks of pyelonephritis produced progressive renal damage and increasing azotemia. Rack's report does not include operative details, but the anastomosis was effected through an anterior abdominal incision.

In both our patients the possibility of placing the opposite ureter in the small bowel loop was considered seriously. It was not thought wise to effect this change, because of the satisfactory drainage and the integrity of the contralateral kidney in both patients. Furthermore, neither patient desired interference with what was considered an existing satisfactory solution of the problem, and neither one believed that the care of a second cup would add materially to the burden. The further course of each patient has demonstrated the wisdom of each one's choice.

CONCLUSION

Experience with these 2 patients and a review of those previously reported indicates that ileal replacement for part, or all of the ureter is a feasible and entirely satisfactory procedure.

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CLINICAL AND PATHOLOGICAL STUDY OF PYELONEPHRITIS IN PUERTO RICO: REVIEW OF 2,800 AUTOPSIES AND 1,887 CLINICAL RECORDS

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A perusal of the medical literature discloses that the nonspecific infections of the kidney outrank in frequency the other known ailments affecting these organs. It is also evident that pyelonephritis must be considered a dangerous disease because of its peculiarity of going through periods of latency which vary from months to years. In other instances the disease remains unrecognized in view of the fact that its clinical manifestations may be minimal, not related to the urogenital system and sometimes not fully evaluated. Last but not least it is an unfortunate fact that the treatment of this disease very often is incomplete or inadequate, some patients time and again failing to recognize that repeated and careful followup studies are usually necessary and that if satisfactory results are to be expected and obtained, therapy must be prolonged. The resentment that many patients exhibit to the natural expense that results from the treatment of pyelonephritis is probably a contributory factor of great importance.

Most authors are in agreement that often enough the onset of pyelonephritis can be traced without difficulty to the period of early infancy or childhood, the disease manifesting itself in one way or another late in life after periods of latency. There is also enough evidence available to convince the most optimistic that pyelonephritis is sometimes an incurable disease, regardless of the zeal and interest exercised and directed towards obtaining a cure. The ultimate results among these patients are renal insufficiency with or without hypertension, uremia and death.

Found among patients of all ages, sex and race, pyelonephritis can usually be promptly diagnosed in the acute phase; when the disease has reached a chronic stage its recognition offers no great difficulties if a comprehensive urological survey is undertaken. Not infrequently the clinical picture and laboratory findings are misleading and one needs to exercise a great deal of ingenuity, intuition and painstaking efforts to establish a correct diagnosis. We agree with Taylor[1] that in these questionable cases empirical therapy should be carried out.

Until the discovery of the chemotherapeutic and antibiotic agents the treatment of the urinary tract infections, specially pyelonephritis, left much to be desired. Many patients so afflicted suffered for many years or died from the ravages of this disease. Undoubtedly we all have been witness in the past and occasionally nowadays of patients with pyelonephritis, acutely and desperately ill, some of them passing away while when by force we had to sit in silent impotence.

[1] Taylor, R. D.: The diagnosis and treatment of pyelonephritis. Med. Clin. North Amer., **39**: 957–963, 1955.

During the last two decades a score of new drugs has been added to our modern therapeutic armamentarium opening hence the path to bright avenues of hope in our dealings with urosepsis. The therapeutic successes that are acknowledged and that were not seen in the past are many and if it is true that the overall picture and the fate of many patients suffering and doomed to die from pyelonephritis have been considerably changed for the better, it is indeed a sad reality that the natural immunity to these drugs observed in some bacterial strains and the resistance developed by others have curtailed and shadowed to a greater or lesser degree our initial optimism and expectations.

Nesbit[2] has very wisely said that "An intelligent approach to the management of urinary tract infections at any age must therefore include a philosophy of therapeutic failure as well as success." In the light of present knowledge about this subject we must accept failures when they present themselves, but defeat should not be accepted until all the available means of examination and therapy are exhausted.

How often are the resources at our disposal employed to their full capacity and how frequently is hope given up prematurely is hard to state and evaluate. In the experience of all who have studied pyelonephritis one fact merits significant consideration; namely, that the rapidity of subsidence of the symptoms of acute pyelonephritis and of the exacerbations that are prone to occur during the chronic stage when treatment with chemotherapeutic or antibiotic agents is begun, has led many to be too optimistic about considering an infection cured when actually it was not. This premature optimistic attitude, we believe, should be condemned because, as well as others who have studied and are interested in this subject, we have often observed among our patients that pyelonephritis is a disease difficult to cure.

Wishing to evaluate the incidence of pyelonephritis in Puerto Rico and of determining what may be the prevailing successes and failures with the present day management of this disease, we decided to review the clinicopathological material on pyelonephritis at our disposal, this being the first study covering this subject to be carried out in Puerto Rico.

PATHOLOGY

The presence of bacteria within the renal parenchyma is responsible in the early beginning for patchy areas of inflammation extending from the cortex to the medulla and renal pelvis. Interstitial infiltration with inflammatory cellular elements, exudate and minute abscess formation are predominantly seen involving and producing damage to both elements of the nephron. Upon healing, minimal scarring is observed but if not controlled, the infection progresses and with the appearance of new patches of infection further scarring results with additional destruction of the functional units of the kidney leading inexorably to the contracted pyelonephrotic kidney.

[2] Nesbit, R. M.: Acute urinary tract infections in infants and children. Ped. Clin of North Amer., **2**: 771–779, 1955.

TABLE 1. *Autopsies performed by the Department of Pathology, School of Medicine and Tropical Medicine, University of Puerto Rico: incidence of pyelonephritis*

Year	Autopsies	Acute		Chronic		Acute & Chronic		With Nephrolithiasis	
		Case	%	Case	%	Case	%	Case	%
1926–1930	540	1	.18	8	1.5	9	1.7	7	1.3
1931–1938	412	7	1.7	17	4.1	4	.97	4	.97
1939–1944	423	3	.71	6	1.4	2	.47	2	.47
1945–1950	811	3	.37	12	1.2	7	.86	6	.74
1951	614	2	.32	12	1.9	12	1.9	5	.81
Totals	2,800	16	.57	55	2.0	34	1.2	24	.86

ETIOLOGY

The presence of urinary calculi, urostasis, tumors, neurogenic dysfunctions of the urogenital tract and specially distant foci of infection are unquestionable factors that sooner or later permit bacteria to take a foothold in the renal parenchyma through various portals of entry; namely, the bloodstream, lymphatic passages, direct ascent through the ureteral lumen and lastly through a lymphohematogenous route.

ANALYSIS OF PYELONEPHRITIS IN PUERTO RICO

The clinicopathological material used in this study consists of 2,800 consecutive autopsies performed at the School of Medicine and Tropical Medicine by the Department of Pathology under the direction of Dr. Enrique Koppisch, professor of pathology. Criminal and other medicolegal postmortem specimens examined by this department are not included in this report.

This study also comprises a critical review of 1,887 consecutive personal private patients. The information that follows, therefore, includes statistical data from 4,687 clinical records and autopsy protocols.

POSTMORTEM ANALYSIS

In table 1 are found the distribution of autopsies per year group and the incidence of pyelonephritis in the acute and chronic stages.

It is worthy of note in this table that pyelonephritis was complicated with renal lithiasis in 24 instances or .86 per cent of the protocols examined.

In table 2 reference is made to the condensed total for all years, giving an overall incidence of 129 patients with pyelonephritis or 4.63 per cent. It is also significant that pyelonephritis was considered the main cause of death in 23 instances only. Our conclusions from this analysis are that the incidence of pyelonephritis in Puerto Rico is similar to that reported by Bell[3] in 1942 who found an incidence of 1.6 per cent of pyelonephritis in 33,360 autopsies. Prewitt[4] also found 58 instances of pyelonephritis or 8.7 per cent in 667 autopsies and Staemm-

[3] Bell, E. T.: Exudative interstitial nephritis (pyelonephritis). Surg., **11:** 261, 1942.
[4] Prewitt, G.: Pyelonephritis. West J. Surg., **51:** 393–450, 1943.

TABLE 2. *Condensed total for all years*

Year	Total Post Mortems With Pyelonephritis	Pyelonephritis as Main Cause of Death
1926–1930	25 or 4.7%	10 or 1.8%
1931–1938	32 or 7.7%	5 or 1.2%
1939–1944	13 or 3.1%	0 or 0
1945–1950	28 or 3.2%	4 or .49%
1051	31 or 4.9%	4 or .65%
Total	129 or 4.6%	23 or 0.0078%

ler quoted by Lieberthal[5] encountered pyelonephritis in 58 or 4.8 per cent among 1,000 postmortem studies.

PRIVATE PATIENTS

Race. As the percentage of white private patients is higher than in the general population no significant conclusions can be revealed as to racial preponderance of pyelonephritis with this study.

Age. Pyelonephritis was significantly encountered in all age groups. Detailed information on this topic is not included in this report because reference to age will be made in another publication which includes pyelonephritis in children.

A diagnosis of pyelonephritis was made on 289 patients or 15 per cent, 191 or 66 per cent being women and 98 or 34 per cent men. A diagnosis of acute pyelonephritis was made in 33 patients or 1.8 per cent. The incidence, although apparently low, is explained on the basis that acute pyelonephritis is usually treated by the family physician, the general practitioner or the clinician, the urologist's assistance being sought, at least in Puerto Rico, when the infection persists and concomitant genitourinary disease is suspected. The patients with acute pyelonephritis were seen during the first episode and the possibility of dealing with an exacerbation of an old process was carefully discarded as far as possible from the history. In this group complete followup studies are available on 21 patients or 64 per cent, but in the remaining 12 or 26 per cent final studies were not possible because these patients either failed to return as soon as the acute symptoms subsided or perhaps medical advice and treatment were sought elsewhere.

A complete cure was observed in 19 or 57 per cent of patients after obtaining repeated negative urine cultures, stained urine sediments and when the patients were free from urogenital or systemic complaints. In two patients or 6 per cent the urinary infection persisted and passed into the chronic stage, the responsible organisms being Pseudomonas in one instance and E. coli in the other.

A diagnosis of chronic renal infection was made in 256 patients or 13.8 per cent. The infection was limited to one kidney in 82 patients or 32 per cent while in the remaining 174 patients or 68 per cent both kidneys were considered to be involved upon finding positive urine cultures and Gram stains of the sedi-

[5] Lieberthal, F.: Pyelonephritic contracture of kidney. Surg., Gynec. & Obst., **69:** 159, 1939.

ment of urine or when there was conclusive evidence of renal inflammation on pyelographic studies.

The incidence of unilateral renal infection may appear too high but in this figure are included patients with unilateral renal lithiasis.

Among the stone patients with infection 43 or 72 per cent were men and 17 or 28 per cent women. In this group the ratio of infection is reversed this being explained by the fact that among our series of patients with stone the prevalence of calculi has been found to be greater in men than among women in a proportion of 3:1. In the review of this series of 1,887 patients renal calculi were found in 133 or 7.1 per cent; and as in 60 or 45 per cent of patients renal lithiasis and pyelonephritis were found concomitantly, this finding leads us to believe that, perhaps, in Puerto Rico renal infection may be a prominent contributing factor to stone formation.

BACTERIOLOGY

Routine urine cultures and Gram stain studies of the urine sediments were done on all patients and sensitivity tests ordered only when indicated.

Table 3 shows in order of frequency the various offending organisms isolated from the urine of 289 patients suffering from pyelonephritis. Mixed infections were encountered in 36 instances or 12 per cent.

In table 2 it is evident that Escherichia coli was the most prominent organism responsible for pyelonephritis. Gram negative bacilli accounted for renal infections in 174 instances or 54 per cent against the cocci group which were isolated in 151 patients or 46 per cent.

After this study was begun we thought that it might be of some interest to review the last 464 consecutive urine cultures with sensitivity tests done in our office.

Of 454 urine cultures performed, 216 were found negative. Many in this sterile urine group were followup studies of patients under treatment.

In table 4 the various organisms isolated are shown in order of frequency, and

TABLE 3. *Bacteria isolated in 289 patients with pyelonephritis*

1. E. coli	94
2. Non-hemolytic Staphylococcus	38
3. Proteus	31
4. Alcaligenes faecalis	28
5. Non-hemolytic Streptococcus	26
6. Hemolytic Staphylococcus	22
7. Pseudomonas	20
8. Aerobacter	18
9. Hemolytic Streptococcus	14
10. Staphylococcus albus	13
11. Paracolon	10
12. Alpha Streptococcus	10
13. Klebsiella	1
Total	325

TABLE 4. *Organisms found in 454 consecutive urine cultures with sensitivity studies*

	Number	Pen.	Erythro.	Terra.	Tetra.	Aureo.	Chloro.	Strepto.	Gantrisin	Fur.	Resistant†
1. E. coli	43	1	0	20	21	19	38	30	9	39	0
2. Alka. faecalis	41	11	20	7	5	6	24	8	2	25	2
3. Streptococcus	34	5	22	6	7	7	20	8	2	20	1
4. B. proteus	28	0	0	0	0	0	25	16	5	19	0
5. Paracolon	24	0	0	3	4	2	18	13	3	16	1
6. P. aeruginosa*	21	0	0	0	0	0	5	11	0	5	8
7. Klebsiella	20	0	0	5	5	3	15	8	1	19	0
8. Staph. albus	12	6	3	3	4	4	4	3	3	5	1
9. Staph. aureus	12	12	4	2	1	1	7	5	0	9	0
10. Micro. tetragenus	1	0	0	1	1	1	1	0	0	1	0
11. Yeast	2										
Total	238	35	49	47	48	43	157	102	25	158	13

Sterile urines—216
* Slightly susceptible
† Resistant to all tested drugs

the sensitivity to various drugs tested noted. It is at once striking that furadantin and chloromycetin were the only two drugs to which most of the strains of bacteria isolated in culture media were sensitive, the third on the scale being streptomycin. Interesting enough is the marked decrease in the incidence of sensitivity of the organisms identified to the other drugs tested. Eight strains of Pseudomonas aeruginosa were found to be resistant to all tested drugs while in 13 other instances the bacteria were considered slightly susceptible to streptomycin, furadantin and chloromycetin.

The use of chloromycetin in Puerto Rico has been greatly reduced as a result of the unfavorable reactions that have been reported during the last few years. This in part may explain the lack of possible acquired resistance of bacteria to this drug. In relation to streptomycin we are at a loss to explain the high incidence of sensitive strains inasmuch as the drug is used extensively in all medical circles for urinary and other septic conditions.

We have had an excellent experience with furadantin.* Most of the acute infections or exacerbations promptly subsided when the drug was administered and well tolerated by the patients.

We have had very sad and regrettable experiences with polymixin B and as a result of this have excluded it from our therapeutic armamentarium using it only in extreme cases. That is why we did not use it routinely in our sensitivity studies.

SYMPTOMS

The symptoms of acute pyelonephritis are easy to recognize but during the chronic stage its manifestations may vary considerably (table 5). Although a combination of symptoms was often present among the patients studied the

* Furadantin has been generously supplied to the Urology Service of the School of Medicine by the Eaton Laboratories, Norwich, Conn.

TABLE 5. *Symptoms leading to a diagnosis of chronic pyelonephritis in 256 patients*

		%
1. Burning during urination	59	20.0
2. Microscopic pyuria	52	18.0
3. Microscopic hematuria	28	9.7
4. Acute renal colic	21	7.3
5. Lumbar pain dull in character	17	5.9
6. Chills and fever	17	5.9
7. Loss of weight and tiredness	12	4.1
8. Gross hematuria	10	3.4
9. Gross silent pyuria	8	2.8
10. Albuminuria	8	2.8
11. Lumbar and bladder pain	2	0.69
12. Blurred vision and fatigue	1	0.34

prominent and outstanding complaint was selected and noted in this table in order of frequency.

Burning during urination and microscopic pyuria were the most frequent symptoms and findings leading to a diagnosis of pyelonephritis followed by microscopic hematuria. The eight cases of chronic albuminuria were of interest because the diagnosis was established with the aid of the Addis count in all eight.

Blurred vision and fatigue were the sole complaints of a 28-year-old woman without a previous history of any illness. When referred to us she had moderate elevation of the blood pressure. The Addis count was positive and pyelographic changes of pyelonephritis were evident. Her phenolsulfophthalein excretion was 1.8 per cent with 8 per cent of urea clearance. The creatinine and blood urea nitrogen were 10 mg. and 190 mg. respectively. Four years after establishing a diagnosis of pyelonephritis the patient died in uremia. This case history is striking because the patient was in marked azotemia for several months and almost free of symptoms and furthermore, from the history, symptoms of urinary infection were not elicited.

PERPETUATING FACTORS

In 160 patients, or 63 per cent, chronic pyelonephritis was unquestionably perpetuated by obstructive factors. The 60 patients with renal or ureteral calculi are included among the obstructive factors. In a forthcoming publication on the study of urinary lithiasis in Puerto Rico we shall attempt to establish a relation between lithiasis and infection; therefore the subject will not be discussed at present.

In table 6 it is shown that among 256 patients with chronic pyelonephritis perpetuating factors were encountered in 252, or 98 per cent. In four instances those conditions responsible for chronicity were not found. Neither were they encountered in two of the acute cases.

From these figures we conclude, therefore, that innumerable conditions of the genitourinary tract, congenital or acquired, if not promptly recognized and cor-

TABLE 6. *Factors responsible for chronicity in 252 patients*

		%
1. Renal calculi	60	21.0
2. Contracted vesical necks or median bars	46	16.0
3. Inadequate treatment	31	11.0
4. Urethrotrigonitis	25	8.6
5. Distant foci	19	6.5
6. Nephroptosis	18	6.2
7. Benign prostatic hypertrophy	17	5.9
8. Chronic prostatitis	5	1.7
9. Ureteropelvic obstructions without calculi	4	1.4
10. Carcinoma of prostate gland	4	1.4
11. Renal tumor	4	1.4
12. Ureteral stricture	4	1.4
a) Unilateral, 3		
b) Bilateral, 1		
13. Pyelogenous renal cysts	3	1.0
14. Urethral strictures	3	1.0
15. Stricture of the external meatus	3	1.0
16. Neurogenic bladder	2	0.69
a) Transection, 1		
b) Spina bifida, 1		
17. Polycystic kidneys	2	0.69
18. Contracted T. B. bladder (rt. nephrectomy)	1	0.34
19. Ureterovesical fistula	1	0.34
Total	252	

rected will be responsible sooner or later for the development of infection which may become chronic.

DIAGNOSIS

Without taking into consideration the source or reason whereby patients sought medical advice a complete urological examination was carried out. This included history, physical examination, urine cultures, Gram stains, cystoscopy, pyelography (descending, ascending or both), renal function tests and the Addis count. We are convinced that the Addis count is not only an extremely valuable adjunct to establish a diagnosis of chronic pyelonephritis but also a helpful index in determining therapy and prognosis.

TREATMENT AND RESULTS

Nephrectomy proved to be a curative procedure in 19 patients or 32 per cent of the 60 cases with unilateral chronic renal infection. The removal of renal or ureteral calculi in 27 patients resulted also in the sterilization of the urine. In the remaining fourteen patients or 23 per cent, renal sepsis persisted requiring secondary nephrectomy in nine. In 5 patients the renal function is stabilized but the infection persists. These patients are under prolonged lifetime treatment, as advocated by Taylor.

In the remaining 191 patients surgical intervention was necessary in 80 or 42 per cent. An apparent cure of infection was obtained in 37 following therapy with antibiotics and chemotherapeutic agents for periods varying from one month to two and a half years.

Of the remaining 112 patients eight died from their malignancy (4 kidney tumors and 4 carcinomas of the prostate). We have lost track of 93 patients.

SUMMARY

Pyelonephritis is one of the most common diseases affecting the kidneys. Although a rather silent disease its consequences may be disastrous if not adequately controlled. Antibiotics have aided immensely in the treatment of urosepsis, but in spite of their use pyelonephritis continues to be a most difficult disease to control.

An analysis of 4,687 clinical records and autopsy protocols was made to determine the incidence, etiology, clinical picture and complicating factors of pyelonephritis in Puerto Rico. Detailed information on 352 urine cultures and bacterial sensitivity to different drugs was included.

CONCLUSIONS

Histological evidence of pyelonephritis was found in 4.6 per cent of 2,800 autopsies.

Pyelonephritis was found present in 15 per cent of 1,887 consecutive cases seen in our urological service.

E. coli continues to be the most common organism cultured from the genitourinary tract, but the incidence of bacteria of the cocci group seems to be definitely on the increase.

The three most effective drugs as determined by bacterial sensitivity *in vitro* were furadantin, chloromycetin and streptomycin.

Obstructive uropathies were by far the most common perpetuating factors found in our study but notwithstanding the beneficial effects of antibiotics, pyelonephritis continues to be a very difficult disease to control and eradicate.

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RECENT ADVANCES IN THE MANAGEMENT OF THE INTERSEX PATIENT

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The clinical basis of this paper is a series of 44 intersex patients seen at the Research and Educational Hospitals and Clinics of the University of Illinois Medical School. The study and care of these patients has always been a cooperative project involving many people, and I wish here to acknowledge my indebtedness particularly to Dr. I. P. Bronstein, head of the Endocrine Clinic of the Pediatrics Department, as well as to Drs. Ira Rosenthal, Elizabeth McGrew and many others who all worked together in the study and treatment of these patients. The total number of patients is divided into groups as follows:

True hermaphrodites	5
Male pseudohermaphrodites	11
Female pseudohermaphrodites	0
Adrenogenital syndrome	
females	22
males	9
Gonadal dysgenesis	5
Testicular hypoplasia	1
Total intersex	44

Approximately 20 years ago Dr. Hugh H. Young finished his book entitled GENITAL ABNORMALITIES, HERMAPHRODITISM AND RELATED ADRENAL DISEASES which was published in 1937. This is unquestionably the best book on the subject in English, or any other language. It summarizes well all of the knowledge then available relating to this group of patients. It is a landmark in the history of this subject and is still a most valuable source book for the history, basic anatomy, pathology, and clinical features of these conditions.

There have been, however, a number of very important changes and additions to our knowledge in the intervening years. Even the terminology is changing and the term, intersex is becoming more widely used rather than the old term, hermaphrodite. The terminology is not yet rigidly fixed and in view of some of the changes we will mention later it would seem that an entirely new classification may have to be set up.

Most fundamental is the change in the idea of what sex is and how it is determined. Twenty years ago, sex was a fairly well defined state, which was determined by the histological nature of the gonads. While some of the sexual characteristics were known to vary from the normal patterns, such variation could not in effect alter a person's sex as indicated by the gonadal pattern. It was

known that the psychic pattern might vary from the gonadal type and that it could be very much influenced by training. Also, it was appreciated that every individual formed and excreted some hormones of the opposite sex, and that every one was to some degree a mixture of characteristics from both sexes. However, it was felt that the gonad was the definite arbiter and final determinant of sex.

The change in the idea of what constitutes a person's sex has been evolving for many years and some findings of the last few years have made most necessary a revision of our thoughts on the subject. It is not easy to define just what sex is as it applies to an individual. It is almost a philosophical as well as a medical question and I think we can best approach it by reviewing first what attributes or features determine sex.

The first and most basic feature which determines sex is the chromosome pattern of the individual's cells. Briefly, we recall that the sex chromosome in females is made up of two X elements, while the male sex chromosome is made up of an X and a Y element. When the sex chromosome divides during maturation, each ovum, therefore, carries an X element while half the sperm carry an X and half carry a Y. Depending on which kind of sperm unites with the ovum at fertilization, the resulting individual carries an XX or XY sex chromosome in each of its cells. Up until the last year or so, it was thought that the individual's clinical sex always corresponded to the chromosomal sex. Recent evidence indicates that this is not so. For instance, patients with gonadal dysgenesis, formerly called ovarian agenesis or Turner's syndrome, who were considered to be female, have now been found in most cases to have the XY chromosome complex. On the other hand, patients with testicular hypoplasia and the so-called Klinefelter syndrome (or more properly Bronstein-Klinefelter syndrome, since it was first described by Dr. Bronstein), have male characteristics, but have been found in some cases to have a female XX chromosome complex.

The next most important factor that determines sex is the nature of the gonads. For many years, as mentioned before, this was considered the best indicator of the true sex of the individual. The primitive gonad is indeterminate, and during development there are periods in which the gonadal pattern of first one sex and then the other is predominant. The conversion of a gonad of one type to that of another type is not entirely out of the realm of possibility (and has been accomplished experimentally in insects).

The next factor in the determination of sex is the hormonal pattern. The hormonal effect on the growth and development of various tissues and organs is one of the mechanisms by which the gonads regulate and influence sexual development. However, we find that hormones from extragonadal sources also can drastically alter the development of sex features.

The most obvious group of factors determining clinical sex are the sex organs; including the internal and external genitalia and the secondary sex characteristics. Most important of these are the external and internal genitalia; namely, the duct and glandular structures and copulatory organs. The secondary sex characteristics include the general overall body structure, breast development,

and many lesser features, such as laryngeal development, voice, skin character, hair pattern, distribution of adipose tissue, etc.

There is yet another factor determining sex, and that is the psychic pattern. We know that this is influenced by the hormonal pattern as well as by the upbringing and experience of the individual. However, we know that it is a very uncertain guide as to true sex, as proven by the many individuals with homosexual tendencies.

After considering these factors which go into the determination of sex, we are in a little better position to define sex. The definition we have evolved is not an exact one, but we think it states the situation as well as our present knowledge allows. The definition is as follows: Sex is the overall state of body and mind by which the individual conforms to the male or female standards of normality in the named sex-determining factors. It is an algebraic summation of these factors in which no one factor supersedes the others. In other words there is no single conclusive determining factor. Every individual we know is a mixture of characteristics of the male and female, and it is the algebraic sum or preponderance of all these factors which determines sex, and not any single one of them.

Discussing these factors individually, we find that the greatest recent change has been in the study of the chromosomal pattern.

The chromosomal pattern can now be determined quite accurately. The method was discovered by Dr. Murray L. Barr of the University of Western Ontario in Canada about 1950 and was applied by him and his associates to determination of sex in intersex cases within the next couple of years. Dr. Barr has examined many skin biopsies for us and his method has been used by Dr. Elizabeth McGrew at the University of Illinois with excellent results (fig. 1, *A*). Accumulating experience confirms the accuracy of the method. More recently, mouth (fig. 1, *B*) (and vaginal) scrapings have been used and it seems that this method is just as accurate as the skin biopsy. A group in England (Davidson et al.) has also studied blood smears and they have detected a sexual difference in the nuclear pattern of the neutrophil leukocytes. As a matter of fact the chromosomal pattern can be determined in the cells of many tissues provided they have been properly fixed. Fixation with formalin tends to shrink the nuclei and clump the chromatin so that Dr. Barr's method cannot be applied. Tissues which have been fixed in Bouin's or Zenker's solutions, or the modified Davidson's solution recommended by Dr. Barr for skin biopsies, will all give satisfactory sections for chromosomal study. Mouth or vaginal scrapings are fixed as for exfoliated cell study in half and half ether and absolute alcohol. Staining of tissue sections is done with H and E and Feulgen stain, while the mouth smears are stained with crystal *echt* violet. The small chromatin mass is identified along the nuclear membrane in a majority of cells in females but in only a small percentage in males.

The gonadal type is determined not only by the chromosome pattern but by separate genes which influence development of the gonad and thus it is possible for an individual to have a chromosome pattern of one sex and a gonad of the

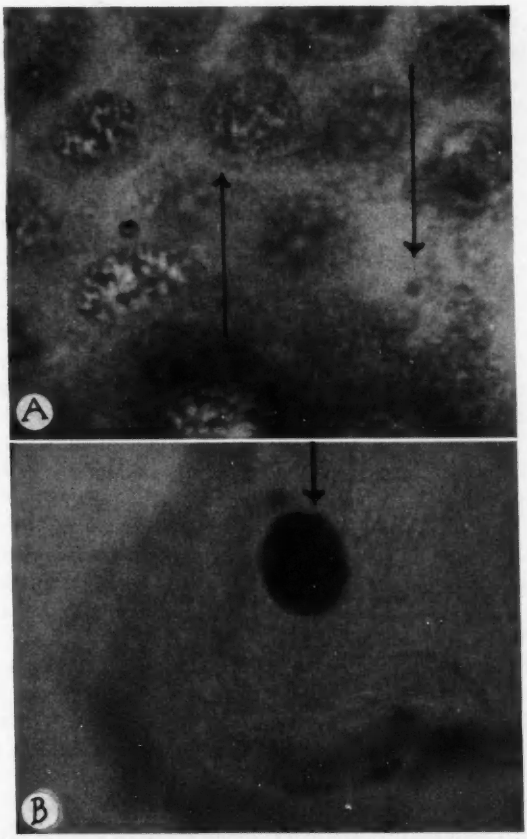

FIG. 1. *A*, skin biopsy showing sex chromatin mass in several nuclei. Case of adrenogenital syndrome. Feulgen stain. Oil immersion. *B*, oral mucosa smear showing sex chromatin mass in nucleus stained with crystal *echt* violet. Oil immersion.

other or, as in so-called true hermaphrodites, gonads of both types with either chromosomal pattern. Gonadal type at this time can be determined only by biopsy and histologic section.

The hormone pattern is now known to be a mixed one in every individual with a preponderance in either direction varying usually according to the gonadal type. The exact role of the hormones elaborated by the fetal gonad in further sex differentiation and in development of the secondary sex characteristics has yet to be determined with certainty. The general hormonal pattern can be determined by chemical tests and can be altered by administration of hormones.

The character of the sex organs, particularly the copulatory organs, is increasingly important in the determination of the proper sex, now that the gonadal

type is no longer the definite determinant. As we all know there is a great variability even in normal persons, in the genitalia and secondary sex characteristics, but in many intersex cases the potential adaptability of the genitalia carries considerable weight in the determination and establishment of sex.

There have been some very excellent recent studies of the psychic factors in the intersex group by Money and the Hampsons. The psychologic study of very young children is a difficult matter, but these authors have examined a large number and have come to the conclusion that a person's ideas of his own sex or his "gender role," become fixed at a very early age, and that attempts to alter it by "change of sex" after early infancy are unwise. We do not feel quite so strongly on this subject as they do. We have had some examples of change of sex in later childhood and even teen age without disastrous consequence.

As to the overall approach to the intersex patient, there are two basic principles. First, the investigative workup should be done just as early in life as possible. Second, on the basis of the findings, a prompt determination of sex should be made. The final assignment of sex in any given individual is made only after group consideration and weighing of all the findings. It is impossible to assign a fixed table of relative values to the various factors.

The genitalia and secondary sex characteristics are not of primary biologic importance but we must remember that their character and development, especially of the copulatory organs, govern the potential adaptability of the individual to one or the other sex and therefore they assume a practical importance far above their biologic importance.

The gonads are probably next most important. The hormonal pattern is less important since it can be clinically altered at will with present day hormone preparations. The psychic pattern is such an indefinite feature in infants and children that it carries much less weight than the organic factors in this group, but in the older child and adult it must be seriously considered.

The chromosomal pattern is the most recent to be used and is in a sense the most basic factor biologically. Still, it is not an entirely true guide in itself, as we see in those groups, previously mentioned, of gonadal dysgenesis and testicular hypoplasia.

The final sex for the individual will be that which fits the gonadal, chromosomal, and genital sex patterns best. In some cases, including the true hermaphrodites, where the genital organs are also indeterminate, the final decision will be most heavily influenced by the potential adaptability of the sex organs to the normal pattern of the sex selected. This may be true even though it does not entirely agree with other factors.

We shall now take up the individual groups and note the recent changes which have occurred. The adrenogenital group is the largest and there has been a most profound change in the handling of these cases. Many males are now found in this category although they are not classified as intersexes and do not concern us directly at this time. In the last few years the discovery that some of these patients also have electrolyte disturbances has added another important and

complicated element to the clinical picture. Apparently the hyperplasia of the steroid-forming elements in some way alters the electrolyte-controlling hormone output so that there is sodium loss and retention of potassium. This may lead to a clinical picture of shock, vomiting, dehydration, etc., which may place these patients, especially young infants, in a critical state. The changes can be confirmed by chemical determination of the sodium and potassium levels in the serum.

Diagnosis in adrenogenital syndrome is now simplified. The finding of the female chromosome complex with an increased 24-hour output of 17-ketosteroids usually establishes the diagnosis. The level of pregnanetriol output can also be done in questionable cases. However, a therapeutic test with cortisone therapy, as introduced by Wilkins in 1950, will confirm the diagnosis if the 17-ketosteroid output drops. If the 17-ketosteroid output does not drop the possibility of tumor of the adrenal cortex must be considered and further study done to rule this out.

If the adrenogenital syndrome is accompanied by electrolyte disturbance the matter is one of more danger to life. Cortisone therapy here also corrects the electrolyte disturbance, supplemented at first by DOCA (desoxycortico-sterone acetate) or percorten (long-acting) administration until the electrolyte levels are brought to more normal range. Surgical treatment now is confined to resection of the enlarged clitoris and vulvoplasty to open the vagina. Surgical resection of the adrenals is no longer necessary in the cases due to hyperplasia.

In the case of adrenogenital syndrome due to tumor, surgical removal of the tumor is the only proper course. Presacral retroperitoneal air insufflation is very helpful in these cases in making a diagnosis of adrenal tumor; also the lack of drop in hormone output with cortisone therapy. We have had one such case with complete recovery following removal of the tumor.

We should mention here that there have been reported a few cases in which there is apparently adrenocortical hyperplasia with electrolyte disturbance but without the adrenogenital syndrome. In other words, the hormones produced are not androgenic so that no sexual effects of importance are noted. In these cases hormonal treatment as just described corrects the electrolyte disturbance and is adequate treatment.

The next largest group is that of so-called male pseudohermaphrodites. In this group also there is frequent error in determination of sex at birth. Many of these patients with hypospadias and undescended testis have been thought to be females and have been raised as such. They usually require abdominal exploration for a complete diagnosis; however, if the gonads are in the groins, biopsy may be adequate in conjunction with cystoscopic and x-ray study of the internal genitalia. Included in this group are individuals varying widely from those with a distinctly male habitus and hypospadias all the way to cases with a very female habitus, gynecomastia, a rudimentary penis and an almost normal size vagina. Differential diagnosis must be made between this group and the so-called true hermaphrodites. Most male pseudohermaphrodites have a gonadal and psychic pattern which is male and usually prefer to be male. Usually their hormonal

pattern is of the male type and correction of the situation usually involves hypospadias repair, orchiopexy and, in some cases, mastectomy.

Female pseudohermaphroditism of the non-adrenal group is the smallest group of all. It is unusual to find a primary intersex with ovaries and we have not seen such a case. Assignment of sex in such cases depends on the adaptability of the secondary sex organs and the correction necessary to adapt them to the assigned sex which is usually female.

The most interesting group historically is that of the true hermaphrodites. These cases have always been of exceptional interest and approximately sixty cases have now been well documented and reported. By definition these individuals have both testis and ovarian tissue. No case on record has ever had both testis and ovary functioning so as to form both fertile sperm and ova. As a matter of fact, most intersex cases of all kinds are sterile. The diagnostic problem in most of these is to determine the sex into which the patient best fits by the criteria aforementioned. The established sex may or may not be in accord with the chromosomal pattern or with the apparent major gonadal element. The secondary sex characters must be taken into consideration in considering the adaptability to the assigned sex. Surgical correction can be accomplished quite satisfactorily in nearly all cases.

The patients now called cases of gonadal dysgenesis were formerly known as ovarian agenesis or Turner's syndrome. These individuals have completely undeveloped gonads and the genitalia and secondary sex characteristics are infantile female. Recent sex chromosome studies reveal that most of them have a male chromosomal pattern; however, in the absence of any gonad whatsoever the female genital pattern develops, apparently by default, as it were. This does not alter the clinical handling of these cases; they should continue as females, with hormone therapy to assist to this end.

The group most recently added to the intersex fold is one made up of certain cases of testicular hypoplasia. These patients present a clinical picture of gynecomastia, aspermatogenesis, but normal Leydig cell development. The first case with hormonal studies was reported by Dr. Bronstein of our group in 1939. In 1942 Klinefelter with others reported 9 cases and his name has since been connected with it. Within recent months Dr. Barr has shown that some of these patients have a female chromosomal pattern and we have had one patient in whom this pattern has been found (fig. 2).

We are currently arranging to review our cases of hypoplasia of the testis seen during past years and expect to find others in that same situation.

In conclusion we may emphasize again the following points. First, the very idea of what constitutes an individual's sex has changed and whereas formerly the gonad type was thought to be the final determinant of sex, now it is felt that sex is the overall summation of many factors; namely, the chromosome pattern, gonad type, hormone pattern, sex organ pattern, and psychic pattern.

These factors should be investigated as early as possible and the sex determined and established without delay.

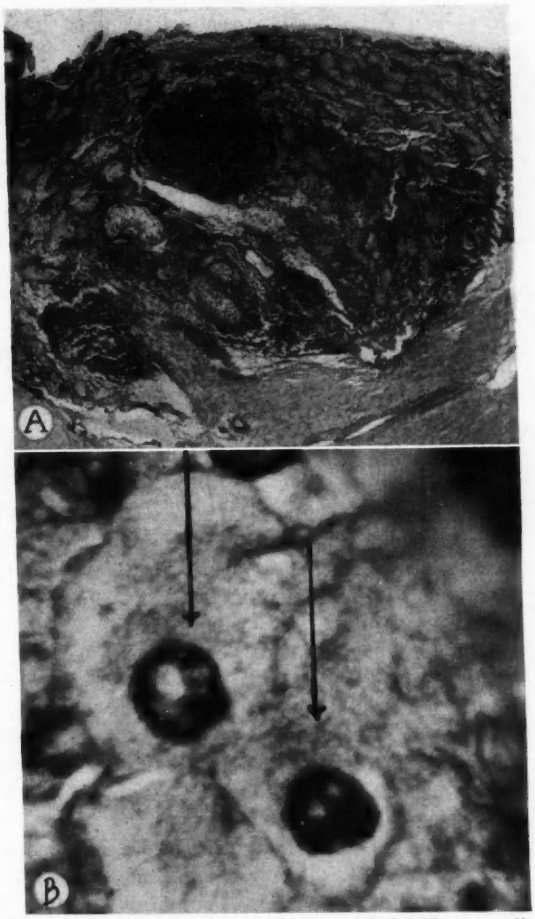

FIG. 2. Biopsy of testis. *A*, case of testicular hypoplasia. Hematoxylin and eosin stain. Low power. *B*, case of testicular hypoplasia. Hematoxylin and eosin stain. Oil immersion showing sex chromatin mass in nuclei.

The adrenogenital syndrome due to adrenocortical hyperactivity has been found to occur fairly often in males as well as females. It is also found to be associated with an electrolyte disturbance characterized by loss of sodium which may lead to a serious electrolyte imbalance particularly in young infants. Diagnosis of adrenogenital syndrome is now made on the basis of chromosome studies and hormone output, surgical exploration being no longer necessary. Treatment of adrenogenital syndrome is medical, by administration of cortisone supplemented at first by DOCA in the early stages in those patients with salt-losing syndrome.

Chromosomal type can now be quite easily determined by means of skin biopsy or oral and vaginal smears.

Many cases of gonadal dysgenesis formerly thought to be female are now known to have a male chromosome pattern. This has not altered the clinical treatment of these individuals.

Some cases of testicular hypoplasia have been found to have a female chromosome pattern; however they still are to be treated as males.

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DISCUSSION

Dr. Grayson Carroll (St. Louis, Mo.): I would like to discuss the paper of Dr. Sanjurjo on pyelonephritis.

I have a concept of pyelonephritis which has helped me in the matter of therapy. There are two types of pyelonephritis: one due to obstruction and another that is due to a hematogenous infection. I think that the type of pyelonephritis which gives us the greatest disturbance is that which is hematogenous.

Therefore, then, it resolves itself into this picture. In the first place, if it is not obstructive, then we do not have many symptoms. Obstructive lesions usually cause pain but with pyelonephritis which is hematogenous there is at first a shower of infection which spreads throughout the kidney with multiple small abscesses. It may cause fever and chills at the time but subsides in a few days.

Then we have a placid period. It is that placid period which is hazardous and dangerous because it is overlooked. At this stage it is a case of the choice of the proper drug and identification of the proper organism.

In the group that was shown by Dr. Sanjurjo, only a small number in the 3000 autopsies had stones. Likewise he did not find many obstructive lesions. The absence of demonstrable obstructive lesions with hydroureter or hydronephrosis should not rule out pyelonephritis. Escherichia coli was found more often than I anticipated.

Staphylococcus and Streptococcus were found frequently which was in accord with our observations.

Meredith Campbell noted that in the wintertime you will find pyelonephritis more often, caused by the Staphylococcus and Streptococcus, since respiratory infections are then common and in the summertime the Proteus or the E. coli, due to the cases of diarrhea that appear at this time.

Dr. Sanjurjo's studies demonstrated the difficulty encountered in the treatment of Pseudomonas. The combination of terramycin and streptomycin will take care of 85 per cent of the Pseudomonas infections; streptomycin intramuscularly given daily and 250 mg. of terramycin given orally 4 times daily. This will not be demonstrated by sensitivity or tube dilution tests.

In the treatment of pyelonephritis the selection of the drug and repeated cultures are most important because when one organism is inhibited another emerges.

The Aerobacter aerogenes is usually inhibited by achromycin. The Proteus is controlled by furadantin. The Streptococcus faecalis is best treated by mandelamine. The Streptococcus hemolyticus and Staphylococcus are controlled by erythromycin or novobiocin.

Sensitivity tests should be considered but cannot be followed blindly. All medication should be carried out for three or four weeks beyond the acute stage in reduced doses.

Dr. David M. Davis (Philadelphia, Pa.): Concerning the paper of Dr. Kiefer,

it is fortunate indeed that the constitutional amendment permitting female suffrage came in time. Otherwise, the problem of determining who was entitled to vote would be impossibly difficult.

However, I am really here to discuss Dr. Sanjurjo's paper. I would particularly call attention to the great preponderance in his series of lesions of a type that will cause lower urinary tract obstruction. Dr. Carroll mentioned that some of these cases were obstructive. I would like to submit that we do not know how many of these cases are obstructive, because we are still in the state of knowledge in urology in which we recognize with assurance only comparatively advanced and late obstruction. In addition, we do not know what is the relation between lower urinary tract obstruction and pressure conditions in the upper urinary tract. It is increase in intraluminal pressure which permits infection to occur and perpetuates it after it has occurred.

In the lower urinary tract in both sexes, but particularly in females, we have very poor methods of recognizing slight and early obstructive lesions, and indeed I would say that this is one of the areas in urology where our knowledge is most incomplete and unsatisfactory. We have no method whatever of determining pressures in the upper urinary tract. Pyelography demonstrates only advanced lesions which have caused marked anatomical changes, and which are obviously the result of long-continued pressure increases.

It is part of urological orthodoxy that blunting of the calyces is the result of pyelonephritis. I submit that we have no evidence whatever to prove that such blunting is the result of pyelonephritis. There is just as much reason to believe that the obstruction which caused the blunting is the effective cause of the chronicity of the pyelonephritis.

The spectacular way in which a chronic infection disappears after the discovery and cure of an obstructive lesion should stimulate all of us to search for such lesions with renewed energy and patience.

Dr. J. Hartwell Harrison (Boston, Mass.): I would like to discuss each of these excellent papers, but do not feel qualified to do so. I wish to thank Dr. Kiefer for bringing to us additional diagnostic criteria, by which we can anticipate the changes in the adrenal cortex which have produced a pathologic state. I think that we must point out from our experiences in the past that there is perhaps a difference in the motivating factors which produce these reactive states in the adult (the acquired state) as over against the developmental condition seen in early life. Hyperadrenocorticism in the adult and the child behaves physiologically and responds differently to therapy. The remarkable results of the treatment of hyperplasia of the adrenal cortex of the child on treatment with cortisone is in sharp contrast as to the limited results of therapy in the adult. We have not been able to cure the adult patient with Cushing's syndrome by medical therapy though some improvement can be obtained. A small number have been improved by pituitary irradiation, but in general it is necessary to resort to surgery. We have studied in the adult the differentiation between hyperplasia and neoplasia of the adrenal cortex. One can accomplish this clinical differentiation with the responses that Dr. Kiefer had mentioned, namely by simu-

lation with ACTH or suppression with cortisone acetate. The malignant growth usually does not show a response to ACTH nor is it suppressed by the administration of cortisone. The differentiation of benign adenoma of the adrenal cortex is not so clear cut by these tests and some response to ACTH may occur as well as some evidence of suppression when cortisone is given. Dr. Kiefer has brought to us another method for studying these pathologic states and for improving our diagnostic methods.

I wish to thank Professor Sanjurjo for his excellent study of the important subject of pyelonephritis. At the Peter Bent Brigham Hospital, owing to the work of John Merrill and the renal group, we are confronted with the problem of many patients with severe renal failure. It is significant how many of these are due to untreated or neglected pyelonephritis. It should be emphasized that the average practicing physician today in treating a patient with acute prostatitis in the male, or acute pyelonephritis in the female, utilizes bacteriostatic therapy for a short period of time, usually no longer than seven to ten days. Much longer periods of active therapy and close observation are necessary to prevent these patients from developing chronic infection. At the same time search for foci of infection is probably not made routinely and it is our responsibility as urologists to educate our confreres with respect to the great importance of these measures.

Dr. Carroll's remarks regarding the identification of organisms deserve great emphasis. By using the pour plate technique the most accurate identification of bacteria can be made and the most significant organism determined by doing colony counts. This bacteriologic technique permits more accurate sensitivity studies which reveal partial inhibition of bacteria as well as complete inhibitions. When the bacteriologist sends you a report that the organism is not completely sensitive to a drug, it can be demonstrated frequently that there is a partial inhibition by this antibiotic which clinically or in vivo may be complete. The efficacy of combined therapy with sulfonamides and antibiotics simultaneously is well known and when guided by accurate sensitivity studies, gives the best results in the treatment of acute pyelonephritis and the prevention of the development of chronic pyelonephritis.

Dr. John K. Lattimer (New York, N. Y.): May I ask Dr. Kiefer at what age he thinks the gender identification factor is so well established that we must not reverse it?

Dr. William J. Baker (Chicago, Ill.): We have been doing quite a bit of this ileal work another way, and two questions arise in my mind.

Most of the instances in which we have taken an ileal segment and transplanted ureters into it, the patients have a stormy postoperative course, and I would like to ask you just what kind of postoperative course your patients had when you substituted ileum for ureter.

My second question is related to whether you leave a catheter in that new ureter, and just how do you divert that urine to prevent back pressure on the kidney? This ileal loop puts off quantities of mucus, and we have irrigated loops for about 20 or 25 days after operation, to obviate blockage by the mucus secretion.

I enjoyed your paper very much, Dr. MacDonald.

DR. FRANK HINMAN, JR. (San Francisco, Calif.): I would like to discuss Dr. Kiefer's paper, because I don't think that we have got excited about it enough, have not got excited enough about the great advances that have been made in the last two or three years.

One advance is the skin biopsy which has allowed us to determine what, if you will, the Lord intended the patient to be, whether male or female.

When you think about it, Jost, in France, has done the critical experiment. Now, for the first time, we can tie all hermaphroditism into one bundle. We can get all the rest together in a group.

I don't know whether you know what Jost's experiment was, but it's a classic experiment done back in 1950, and he's still working on it. He takes rabbits during their early pregnancy, opens the uterus, opens the fetus, and takes the fetal gonads out, and then closes them both back up again. The time when you take the male gonads out will determine what sort of intersex you get. If you take them out, very, very early, you will get a female fetus, female as far as the rest of the genital characteristics are concerned. If you take them out a little later, you will get one of the intersexual states, and if you take them out after a certain period you will get normal male genitalia.

Now, that's what's happening with these individuals whom we saw today. Cases of gonadal dysgenesis and certain of the male hermaphrodites—those that we call the "hairless Venus" type—are males but completely feminized.

Then we see gradations of intersex which have hypospadias and other abnormalities of the testes, often with retained testes, all the way down to the normal male.

To me, now, for the first time, we see this group arising as an experiment of nature in which the testis fails in early fetal life to assure its role as "organizer" for male differentiation, leaving the individual to the influence of the underlying female orientation. Thank you.

DR. O'CONOR (Chicago, Ill.): I would just like to ask a question of this learned group here. Has anyone in this room got a rational explanation for the mutation of organisms in urinary infection as a result of modern antibiotic therapy?

If you have, I'd be delighted to hear it, and I think it would be very revealing to all of us. I have talked to bacteriologists all over this country. I have been trying to postulate some experimental work that we can do to clarify this thing, and I have gotten absolutely nowhere.

PRESIDENT HECKEL: Does anyone have?

(No one responded.)

DR. S. A. MACDONALD (Montreal, Canada): I would like to thank Dr. Baker for his discussion. Our experience has been limited to the construction of two ileal ureters and four such bladders. Unfortunately there has not been time to refer to this latter group of patients.

In the ureteral patients, only one serious postoperative complication occurred. This was due to a fibrinous type of peritonitis as a result of which a small bowel obstruction occurred. The involved ureters are almost invariably infected and

some degree of peritoneal contamination cannot be prevented. In our patient the abdomen was reopened about the twelfth postoperative day and two adherent loops of ileum were separated digitally. An enterostomy was done and the patient's further course was uninterrupted.

Mucus production can be troublesome and determines the type of collecting apparatus to be employed. It is essential that the equipment possess a large aperture so that mucus obstruction will not occur. The standard Singer cup is not suitable because of its inadequate outlet. It has been our practice to remove the top of this device and cover it with a piece of thin rubber tightly stretched to produce a waterproof seal. This removable cup permits the evacuation of mucus as necessary.

In the postoperative period pressure necrosis from an indwelling bag catheter must be avoided. Prolonged catheter intubation can produce uncontrollable hemorrhage which has been reported by Rack in one patient.

DR. SANJURJO (San Juan, Puerto Rico): I think I can summarize Drs. Carroll and Harrison's comments as follows: Regardless of the causative factors, we are most concerned with patients with latent pyelonephritis: patients whom we consider neglected either because physicians ignore the fact that one negative urine culture does not mean cure or because the patient does not realize that the treatment of pyelonephritis may be prolonged. This fact is borne out by daily experience. We have seen patients with five consecutive negative urine cultures. The sixth one was again positive and further treatments lasting several months were necessary. This is observed often enough, but very few patients who know that a urine culture has been negative on two or three occasions are willing to go to the expense of further studies mainly when they are asymptomatic.

The other type of neglected patient is the one in whom on routine urinalysis a few pus or red blood cells are seen and no attention is paid to these findings. Anyone who goes over a number of hospital records will discover that this is so. In our experience many of these patients suffer from chronic pyelonephritis.

Many drugs are known to be capable of controlling pyelonephritis, but there are some patients in whom the infection can not be eliminated regardless of what is done.

I do not think that I can answer Dr. O'Conor's question on the mutation of bacteria, but I would like to mention something that I did in Puerto Rico in the Army when we first used penicillin. Once the diagnosis was established by a smear, we gave an injection of 10,000 units of penicillin. That was the amount given at that time by the Army, 10,000 units 4 times a day. However, we cured about 80 per cent of the patients.

Every hour thereafter we took a smear and did a stain. By the second hour, the gonococci were still present. However, you could see that they were entirely different gonococci. Some of them became very small, others swelled up and their staining characteristics changed, and by the fifth hour they had all disappeared.

Where a recurrence was noticed, it was just the reverse. The abnormal forms were seen first, and then later they developed the normal staining qualities and morphology.

When we began using 300,000, 600,000, or a million units of penicillin I tried to do the same thing, but I was never able to reproduce this initial finding. Maybe smaller doses of a drug contribute to mutation as well as to resistance—I don't know—I just wanted to mention what was observed and noticed back in 1943.

DR. KIEFER (Chicago, Ill.): I'll try to take these in order, if I can.

Dr. Davis' comment was true. This patient whose test I showed you, when we tried to get him back for more smears, was in the Army, where he is now; so he's still a he.

The dose of cortisone, of course, varies somewhat with the age of the child, but that child is on 25 mg. a day. Like any other patient on cortisone, these patients must be watched for intercurrent disease, because they may require special attention. Whether these children will become insensitive to cortisone later on, I don't know. I always feel a little uncertain about that.

Dr. Harrison—as to the tumors in the adults and their reaction to cortisone therapy—the tumors presumably escape or are no longer under pituitary control, and the ACTH tests are not effective in them. I didn't go into that because I was short of time, but we had a case that was completely cured by the removal of a rather large adrenal adenoma.

As for the age that the gender role becomes fixed, it is within six months, according to Money and the Hampsons, but they are psychiatrists, primarily. I think they overdo it, from our clinical experience. Since this list was made up, the sex of a male pseudohermaphrodite, age 17, was changed, but he had known all along that something was wrong, and he was very happy about it and looked forward to the procedure; so there's no psychic trauma there. In fact, because of parental difficulties, there was a lapse of several years between the time the advice was given and the time of doing it. I do not think that the gender role becomes fixed so early in life.

Dr. Hinman commented on the development of gonads. This is very fine for the male ego, because the male is the perfect development. In the gonadal dysgenesis, if you have no gonadal development you end up a female; and males can all smile about that if it makes them feel any better.

SYMPOSIUM ON CRYPTORCHISM

INDICATIONS FOR HORMONAL TREATMENT OF CRYPTORCHISM

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Hormonal therapy for the cryptorchid has been used for 25 years, but one cannot find among the numerous articles any paper which summarizes the indications for its use. The many favorable reports at the onset of hormonal therapy indicated that its use might replace the surgical orchiopexy. To a certain extent this attitude was justifiable, because the surgical orchiopexy at that time was successful only in about fifty per cent of the cases due to short cords and interference with the blood supply to the testis.

Although several hormones, such as estergin, androgin, pituitary and thyroid extracts, have been used, it is generally accepted that the hormone which supercedes all others is the hormone extracted from the urine of pregnant women. This anterior pituitary-like principle known as APL and pharmacologically as follutin-S is the hormone of choice and is the one universally used. The hormone is found in the blood and urine of the fetus, and is present for 5 days following birth, after which it practically disappears until puberty. The greatest quantity of the hormone appears during puberty, after which there is a gradual diminution until old age.

Normally, the testicles descend into the scrotum during the latter months of pregnancy, and those that have not descended at birth have a tendency to descend at puberty, two periods when there is the greatest amount of the hormone present. The inference to be drawn from the natural existence of this gonadotrophic hormone and the time of the descent of the testis into the scrotum, make it the most plausible factor initiating the descent of the testis. The real active force which causes the testis to pass through the inguinal canal to the scrotum is the milking action of the cremasteric muscle. This physiological action has been observed by Hart in the kangaroo rat. Lewis severed the nerve to the cremaster muscle in rats and failed to obtain descent of the testes. These experimental observations, when transposed to humans, are rendered more potent by the fact that boys who have an agenesis or a testis which has never passed the internal inguinal ring are found to have a flat and undeveloped scrotum, the result of maldeveloped cremasteric muscle. A boy who has a migratory testis, a pseudocryptorchid, or who at some time has had a descent of the testes into the scrotum will show development of the scrotum and cremasteric muscle on that side.

Our research on the pre-adolescent macaque monkey, which included the sectioning of the cord and scrotum on one side followed by sufficient gonadotrophic hormonal injections to produce descent of the remaining testicle, was accompanied by a widening of the inguinal canal, an enlargement of the cremasteric muscle, increased vascularity of the cord, increased size of the lymph spaces, enlargement of the muscle fibers of the vas, and heaping up of the epithelial cells lining its

lumen. Thus we have initiatory and developmental factors favorable for the descent of the cryptorchid.

The indications for the hormonal treatment of the undescended testis depend upon the location of the testis, whether it is intra-abdominal, within the inguinal canal, ectopic, or whether it might be unilateral, bilateral or absent, whether complicated by a large hernia, hydrocele, or other abnormalities; such as hypothyroid adiposity, hypopituitary dystrophy, eunuchoidism, dwarfism, or pseudohermaphroditism with bifid scrotum and hypospadias. The male and female pseudohermaphrodites without palpable gonads may be differentiated by the cytological sex chromatin epithelial cell tests.

Theoretically, the most favorable cases for the use of the hormone are the bilateral cryptorchids, because without obstruction to their course of descent, their most probable failure to descend was due to the deficiency of the hormone in utero. These are the most difficult ones to treat primarily with surgery because of the short spermatic arteries. The testis has never migrated; and its artery, no matter what its origin, has rarely had an opportunity to elongate sufficiently to reach the scrotum. It has been estimated by several writers before the use of hormones that 20 per cent of the orchiopexies resulted in the loss of the testis because of surgical interference with the blood supply. The testes in these bilateral cases are less likely to show anatomical dysgenesis than the unilateral cryptorchid, and offer greater percentage of potential physiological normal development than the unilateral cryptorchids. Gross states that 79 per cent are spermatogenic.

Other conditions in which hormonal therapy is advocated may be found in cryptorchids associated with hypopituitary, hypothyroid, eunuchoidism and dwarfism. Many of these cases are treated by endocrinologists. It seems to be the opinion that thyroid adiposities with gonadal dysgenesis should have thyroid treatment before or along with gonadotrophic hormone, and that the treatment be carried over a longer period of time using much larger amounts of hormone than for the uncomplicated cases. These cases demand basal metabolism tests and a correction with extracts of pituitary or thyroid as needed. Not all adiposity cases have thyroid deficiency for some only require limitation of calorie intake along with hormonal therapy. These cases require the attention and services of both the endocrinologist and the urologist.

In the case of unilateral cryptorchid, we have a different problem. Both testes have been theoretically subjected to equal opportunities for descent by the action of the hormone in utero, and it would not be expected that more gonadotrophic hormone would induce a descent of these testes. When one testis is retained and the other testis descends into the scrotum, we find at operation one of the many reasons as listed in our text books for the retention. However, a majority of the unilateral cryptorchids are ectopic testes or are associated with hernias and hydroceles. These are not suitable cases for hormonal therapy. However, there are some unilateral cryptorchids which are not palpated or they lie in the inguinal canal not associated with demonstrable hernia or hydrocele which should be selected for hormonal therapy.

The most difficult testis to transplant surgically is the testis whose spermatic artery is of inadequate length. The fact that these so-called short vessels have

not been a problem subsequent to adequate hormonal therapy, that we have not had to leave such a testis in the inguinal canal for a later transplant as some surgeons report; and lastly that for twenty years we have not had to do an orchiectomy because of insufficient length of cord, designates the importance of the hormonal application for these cases. As an adjunct to technical surgical orchiopexy for the bilateral and unilateral cryptorchids with short spermatic arteries, there is no doubt about the value of the gonadotrophic hormone.

The amount of the hormone to be used has been a subject for great debate and varies from a few hundred rat units to several hundred thousand units. In 1934 Aberle and Jenkins, working on monkeys and later on humans, found that 1700 to 4000 units were required to cause a testis to descend into the scrotum. An edema of the foreskin and scrotum almost always preceded the descent of testis by a few days. For the average boy 3000 units given over a 4-week period produces this clinical picture. Robinson and Engle have tried 4000 to 5000 units of chorionic gonadotrophin per day for three consecutive days and then operating if the testis did not descend. Large doses over a long period of time produce precocious sex development, premature union of epiphyses and psychic disturbances, and some authors report a regression in the size of the testes. Erlich has shown that testes which descend after large doses of hormone are uniformly aspermatogenic. Therefore, it is necessary to set a limit for the amount of chorionic gonadotrophic hormone to be used. For 20 years we have been using 250 units given intramuscularly 3 times a week for 4 weeks, and have experienced no adverse effects under this regimen.

There is great variance as to the age of the child when hormone had best be used. Many observers have expressed the view that the earlier the testis is placed in the normal position, the greater will be the opportunity for it to develop and become spermatogenic. Charny and Wolgin have recently published the most comprehensive microscopic study of biopsies of the undescended testicles at various times; such as from birth through adolescence, after spontaneous descent, after hormonal administration, and during and following surgical orchiopexy. They state that the testis shows three stages of development: 1) resting phase from birth to the age of four years; 2) growth phase from four to ten years; and 3) maturation phase from ten years through adolescence. Certainly if there is any virtue in transplanting the cryptorchid for the maintenance of spermatogenesis, it should be done early in the growth phase.

Objections have been made against the use of the hormone because its administration caused more discomfort to the child than surgical procedure. We have not had this experience. Again, the cost of hormonal treatment has been criticized as being greater than the cost of surgical treatment. If such were the case, then undue charges were made and are to be reprimanded. In the use of the hormone the surgeon should always begin with a plan of therapy and execute the program precisely; followed immediately by surgery if the testis does not descend.

Of the 204 cases of cryptorchism recorded in our series since the onset of hormonal therapy, 56 cases were particularly selected for hormonal treatment; 19 left, 20 right and 17 bilateral. Successful results were obtained in three each left-

and right-sided, and two in the bilateral cases, equivalent to 14 per cent of the selected cases so treated.

The hormone is of no particular value in cases with ectopic testis, migratory testis, pseudocryptorchids, agenesis of testis, cryptorchids associated with large hernias and hydrocele or in post-puberty cases.

SUMMARY

The indications for hormonal use for cryptorchids is limited to a selected group, roughly about 25 per cent of all cases. These cases include all bilateral and special unilateral cases, with the expectation of a small percentage of successful descents. Its main value is calculated as an adjunct to surgical orchiopexy, for the selected group of cryptorchids which have short cords and inadequate spermatic arterial length to reach the scrotum.

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INDICATIONS FOR EARLY SURGICAL INTERVENTION IN CHILDREN

DR. HECKEL: Due to a situation beyond his control, it's impossible for Dr. Robinson to be here for this symposium. However, Dr. Frank Hinman, Jr. has kindly agreed to give his presentation.

DR. FRANK HINMAN, JR. (Substituting for Dr. John N. Robinson): What I'm going to give is, I believe, essentially what Dr. Robinson would conclude. His experience is much greater than ours, but I find we have arrived at similar conclusions.

What we all know, I think, is that the results from orchiopexy are disappointing. This could be, as has been pointed out, due either to the surgeon or due to the faulty testis itself. What we did was study a series of 30 biopsies from undescended testes to see what factors were involved in the patient and in the testis over which we would have little control (in contrast to those factors which Dr. Hand brought out, surgical points) as well as the timing of intervention, over which we would have control.

We took these biopsies and compared them with normal biopsies from patients of the same age. We observed, as Dr. Robinson observed, that cryptorchism is not a disease, it's only a symptom. It was also apparent that many of these testes were no good no matter what you did.

Now, there can be three factors, I think, influencing cryptorchism. One would be abnormalities in the canal and we are all familiar with ectopy in Denis Brown's pouch in which the testis lies just outside the canal but cannot be pushed down to the scrotum. That would be a good example of a true ectopic testis.

The second factor is abnormality of the gonad.

(Slide) This is one group from the University of California. You can see that there is a rather high incidence of other abnormalities associated with cryptorchism.

The other point is that the two testes of the same individual can be different. (Slide) This is the right and the left testis in a 3-year-old. Here on the right you can see great abnormalities (indicating), but here, on the left, is a normal 3-year-old testis.

(Slide) And then, of course, next are extreme forms of agenesis, so that no matter what you did with these individuals, you would not accomplish anything.

(Slide) Here's a microscopic picture. Obviously, no matter what you did in a patient such as this, how early you did an orchiopexy or how carefully you did it, you would end up with nothing from a functional point of view.

Then, the third factor is an endocrine abnormality, such as hypopituitarism. I think the only point here is that you avoid treating the cryptorchism and ignore the underlying disease, or else these individuals become eunuchoid.

Then we come to the factors over which we have some control. Cooper was a female anatomist (could that be one of the reasons why not too much attention has been paid to her work?) yet, 25 years ago, she hunted out this very fundamental fact, that the cryptorchid testis isn't necessarily abnormal. It is merely retarded along the normal path of development, and from our sections we can very easily illustrate this.

(Slide) Here is a normal 3-year-old testis, and here is a cryptorchid 3-year-old testis. At this time, except for the difference in staining, there is very little basic difference. I think you can see that both of them are of equal development at that age.

But we go on to 9 years (slide) and now we can see great differences. Here is the normal 9-year-old in the, if you will, growth phase. Here's the cryptorchid 9-year-old. How much more immature is the testis! (Slide) Next, at 12 years, the delay is even greater. Here's the normal 12-year-old section, and here is the cryptorchid, greatly delayed. It's this sort of picture that I would like to leave with you, and I'm sure Dr. Robinson would, too. This testis, if brought down, would have quite a way to go to catch up with its normal mate, or with the normal individual.

This is the picture that we must keep in mind when we decide when to operate.

(Slide) Of course, after puberty, it's too late. This is a 17-year-old. Here's the normal 17-year-old testis, and here's the cryptorchid testis at 17. Obviously, this is irreversible, whereas Dr. Hand has shown that certain of the earlier cases, as shown in the previous slides, are reversible.

So, many of us would feel that getting the testis out of the higher intra-abdominal temperature as early as is feasible—that is, at about the age of six years—is important.

Now, the factor we are discussing is testicular temperature, and I think in the next few years we are going to hear quite a bit more about testicular temperature in relation to infertility. There is some recent work which has followed up the older work on rams. You are all familiar with woolen jockstraps which render rams infertile. If these rams wear this insulation for as short a period as six or eight hours, they can be rendered infertile for a period of ten days to two weeks.

Now, it's interesting that this only occurs on the rams that have relatively little natural insulation. The rams that grow up with a lot of wool in that particular area are not affected by this insulation, but the others are quite influenced by it. I think you are all familiar with the work on jockey shorts as a cause of relative infertility. This is one of the major fields of research in infertility, that is, of contraception by the Japanese method of hot baths, and so on, and, on the other hand, the attempt to increase fertility by throwing away stocks of those shorts.

You will get a good result if the testis is placed in the scrotum early enough and if the individuals are eliminated who are hormonally imbalanced. We feel it is just as easy to operate on these children at 6 years as at 12 years, so we see no great value in delay.

Now, the technique is important. (Slide) I think you are all familiar with Gross's recent publication. I certainly wish we could do as well as this. There is proof of fertility in these individuals, and I think this shows something that Dr. Hand has brought out, that some testes are good, and if you operate on them you will get good results.

As far as the circulation is concerned, this is an injected specimen showing

the delicate endarterial supply to the testis. In our experimental work, we would temporarily obstruct the artery for a period of 1 hour, 2 hours, 4 hours, and 6 hours. If you obstruct it even for a period as short as two hours, which might occur with operative edema, you get this sort of picture 6 weeks after obstruction. (Slide) Damage is great.

Then if you wait (slide), you will get some regeneration. These are germ cells, but I think you can see that they don't compare with those in normal spermatogenesis.

In conclusion, we would urge early operation. That doesn't militate against the use of hormonal therapy, but it is important that hormonal therapy be tried early, and then proceed with the operation.

PRESIDENT HECKEL: Now, I don't know how you feel about it, but I think anybody who can get up and give an extemporaneous speech like that—I don't think Frank knew fifteen minutes before he got up here on the floor that he was to do the pinch-hitting. John was to send his paper by air mail special delivery, and it didn't arrive, and I got a signal that Frank would be willing to pinch-hit for him.

UNDESCENDED TESTES: SURGICAL PROCEDURES

JOHN R. HAND

The earliest attempts to bring the undescended testis to the scrotum were one-stage procedures. The first is attributed to Koch who, according to Rosenmerkel, in 1820, used a suture to fix the testis to the fundus of the scrotum. Schüller, in 1881, recognizing the need of lengthening the spermatic cord, divided the vaginal process, then placed the testis in the scrotum and anchored it with a stitch. Bevan, in 1899 and 1903, carried the principle further. He removed the vaginal process from the cord, separated the cord from the posterior peritoneum above the internal ring, and freed the vessels and vas from the constricting fibrous bands in the cord. Then he placed the testis in the scrotum without traction and placed a pursestring suture at the top of the scrotum. In 1930, Ombrédanne did a one-stage transcrotal orchiopexy. In his operation the testis is placed on the opposite side of the scrotum and is held in place by means of the elastic septum between the scrotal compartments.

A two-stage orchiopexy was introduced independently by Keetley in England, in 1905, and by Torek in this country, in 1909. In both operations the scrotum is fixed to the skin of the thigh and the testis is fixed to the fascia of the thigh. The two operations differed in that Keetley placed the anchoring suture through the gubernaculum, whereas Torek placed it in the tunica of the testis. In the second stage of each procedure, the scrotum and the testis are released from their attachments to the thigh.

Wangensteen, in 1932, placed the anchoring suture in the testis after the manner of Torek, but brought only the suture to the fascia of the thigh and left the testis in the scrotum. In their procedure, McKenna and Ewert, in 1935, also left the testis in the scrotum, but like Keetley, they sutured the gubernaculum to the thigh.

Kiefer, doing the same type of operation as that done by McKenna and Ewert, in 1951 described a technique for mild, continuous, postoperative traction. It consisted of wrapping a small rubber tissue drain around the scrotal isthmus and attaching the drain to a rubber band stretched down and secured to the thigh with adhesive. In 1931, Cabot and Nesbit achieved adequate continuous temporary traction in their one-stage procedure by means of an elastic band attached to a stay suture passed through the lowest point of the gubernaculum.

Whether it is done by one or two stages, the basic principles of orchiopexy are: 1) to dilate the scrotum for reception of the testis; 2) to get maximum length of the cord so that the testis can be placed in position without tension; 3) to do a high ligation of the vaginal process; 4) to use some means of fixation and traction so that the testis will remain in the scrotum.

While it is desirable to get all the length possible for the vessels of the cord, it is equally desirable not to do more dissection than is absolutely necessary because of the danger of embarrassing the vascular supply. However, the extent of the dissection required is determined by the findings in the individual case. In some

patients, minimal dissection liberates the cord sufficiently to permit placement of the testis in the scrotum or anchoring it to the thigh without tension. In others, not only is extensive retroperitoneal dissection necessary to free the spermatic vessels, but equally extensive dissection must be done to liberate the interlacing fibrous bands between the vessels before adequate cord length is achieved. And in occasional instances the cord remains too short for placement of the testis despite maximum dissection.

In some patients with excessively short cords, Cabot and Nesbit, and later Gross were able to place the testis in the scrotum by a two-stage mobilization procedure. At the first operation the testis is liberated as extensively as the situation permits and placed in position at the lowest possible point. At the second operation, a year or two later, further liberation is accomplished. Schutt was of the opinion that if the cord is too short to allow placing the testis in the scrotum, the scrotum should be brought to the testis, as is done in the Ombrédanne operation.

These last mentioned procedures merit trial, particularly when bilaterally undescended testes with short cords appear to be normal. But whether these or other procedures are done, bringing the testes outside the external rings and placing them as low as possible will preserve at least Leydig cell function. A unilaterally undescended testis with an excessively short cord should be removed. Under no circumstances must a testis be put in the abdomen where it could not be observed for possible development of malignancy.

In a study I recently made, 9 clinically impalpable testes were, on exploration, found in the abdomens of the respective patients. Four testes were easily freed and placed in the scrotums at ages 9, 10, 10 and 12. But 5 had to be removed—2 at ages 15 and 18 because the cords could not be lengthened sufficiently for placement; 2 at ages 53 and 54 because of shortness of the cords and testicular atrophy; 1 at age 36 because of tumor.

While I formerly did the Torek operation almost entirely, I now do a one-stage orchiopexy. The latter operation seems preferable because of the results on followup in my study. This showed the position of the testes was better after the two-stage orchiopexy, but the size and consistency were better after the one-stage operation. In 5 men paternity was attributed to one-stage orchiopexy. There has been no opportunity yet to evaluate paternity after the two-stage operation. But histologic study of tissue removed from 5 testes placed in position by two-stage orchiopexies, from 4 to 10 years previously (at ages 10, 12, 13, 15 and 18), disclosed spermatogenesis in only one-sixth of the tubules present in each section studied. While 2 of these orchiopexies were done late, the other 3 were done at what might be considered favorable ages.

In the operation I do now, an incision is made in the skin over the inguinal canal, beginning just medial to the anterior spine and directed toward the pubic tubercle. Dissection is carried to Scarpa's fascia, which is then incised.

When the testis is retained mechanically outside the external ring, its bursa is intimately attached to the undersurface of this fascia and must be detached from the fascia with care. An attempt is then made to find the point of attachment of

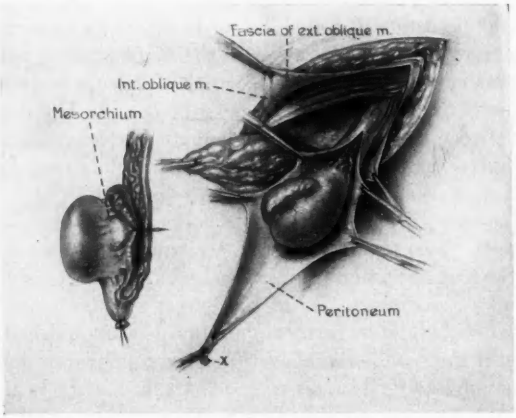

FIG. 1. Elongated peritoneal sac which was directed toward perineum. *X*, fibers of external spermatic fascia projecting beyond bursa. Insert shows vas coursing in mesentery inferior to testis. Danger of catching vas in suture through gubernaculum is evident.

the fibers of the external spermatic fascia (gubernaculum) projecting beyond the bursa (fig. 1). These fibers may attach the bursa in one or multiple positions anywhere along the lateral margins of the pouch as well as to the pubic tubercle. They may be directed toward the peritoneum or scrotum itself and form an attachment at these points. Or, the fibers may terminate at the distal end of the bursa and form no attachment, so that the bursa lies free in the superficial inguinal pouch.

As the bursa is being mobilized, care is taken not to injure any branches of the ileoinguinal nerve coursing toward the scrotum. Doing an orchiectomy on an adult patient a few days ago, it surprised me that dissection of the inguinal canal disclosed no fibers of the ileoinguinal nerve.

To free the bursa from its attachments, the projecting fibers of the external spermatic fascia are incised, after which an opening is made into the inguinal canal by incising the aponeurosis of the external oblique. Traction on the stump of the projecting fibers of the external spermatic fascia elevates the bursa and facilitates freeing it from its attachments to the transversalis fascia, the internal oblique and the transversus muscle. Continuing the dissection cephalad allows freeing of the spermatic vessels well into the retroperitoneal space. I defer opening the bursa until this dissection has been completed.

Stripping the vaginal process and the posterior peritoneum from the vessels permits high ligation of the vaginal process. Additional length may be gained by releasing any fibrous adhesions which may be causing adherence of the blood vessels. If still more cord length is needed, higher retroperitoneal dissection can be carried out by incising the internal oblique laterally, as advocated by Wangensteen, or by splitting the internal oblique, as suggested by Kiefer (fig. 2).

While incision of the transversalis fascia and ligation of the inferior epigastric vessels will add length to the vas, I do not believe length of the spermatic vessels can be obtained in this manner. Because of this, and because of the importance

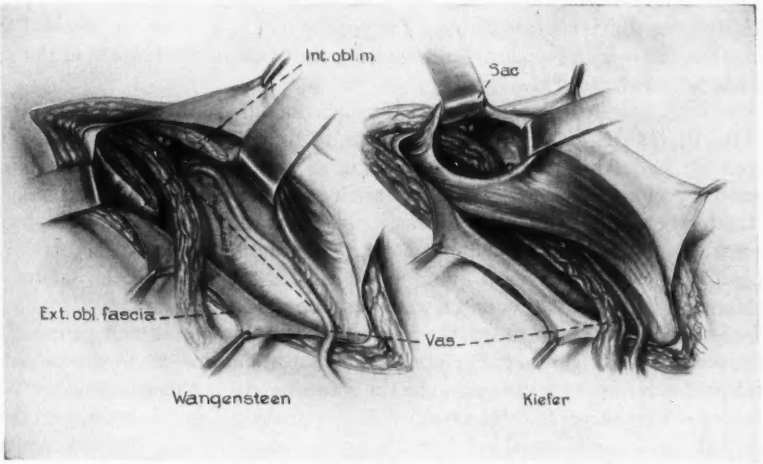

FIG. 2. Procedure for facilitating retroperitoneal dissection of spermatic vessels. In Wangensteen procedure incision is made across internal oblique and transversus muscle. Broken line indicates incision in transversalis fascia. Inferior epigastric vessels course below this fascia. In Kiefer operation, muscle splitting incision is made in line of muscle fibers.

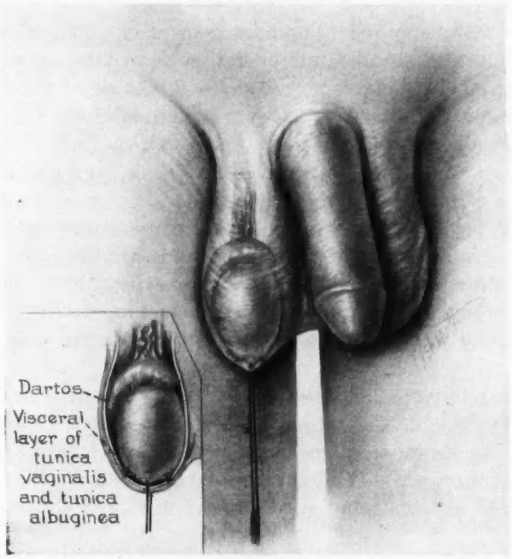

FIG. 3. Method of anchoring testis to dartos in one-stage orchiopexy. Note traction suture. *Courtesy*, Tr. Am. A. Genito-Urin. Surg.

of the transversalis fascia in maintaining a strong abdominal wall, I have avoided incising it. However, if the extreme shortness of the vas left no alternative, I would incise the transversalis fascia and divide the inferior epigastric vessels.

In anchoring the testis in the scrotum care must be taken not to obstruct the

proximal vas which courses through the peritoneum just below the testis. I have found the following procedure for anchoring the testis in the bottom of the scrotum to be satisfactory:

Two catgut sutures are passed first through the dartos, then the visceral layer and the tunica albuginea of the testis. A third suture of silk, for traction, is introduced through the bottom of the scrotum, as near as possible to the septum, carried through the visceral layer of the tunica vaginalis and the tunica albuginea of the testis between the two previously placed catgut sutures, and brought out again through the bottom of the scrotum. The traction suture is then tied to a rubber band which is secured by adhesive tape to the thigh on the side of the orchiopexy (fig. 3). At the end of a week the traction suture is removed.

In repair of the operative site the Ferguson procedure of not transplanting the cord has distinct advantage. Brought out of the wound lateral to the pubic tubercle, the cord lies in a direct line to the scrotum. All the length that has been obtained is thus preserved. However, with this procedure it is necessary to make sure that the inguinal canal is left as strong as possible. When the structures of the inguinal canal appear to be deficient, it is better to transplant the cord and use fascia in the repair instead of catgut.

DISCUSSION

The current controversy regarding management of undescended testes is due not so much to lack of an adequate operation as to "the appropriate age" for surgical placement. Early orchiopexy is stressed because of the recent emphasis on histologic evidence of retarded testicular growth after the age of 5, which is of special importance when both testes are undescended. Deferment of orchiopexy to puberty is favored because of the possibility of delayed spontaneous descent. This occurs in a significant number of testes, and in some instances as late as puberty. Age, however, becomes of secondary consideration when a concurrent clinically demonstrable hernia or torsion demands surgical intervention. At the operation for correction of such a complication, often in the young child, the testes are also brought to the scrotum. Thus, orchiopexy is many times done early even by those who would under other circumstances defer the operation until puberty.

Confronted with impalpable testes or testes palpable either in the canals or at the external rings, the physician today does not have to wait a year or two, or longer, to see if the testes will descend spontaneously. Hormone stimulation will induce descent if there are no complicating factors, and it will, also, contribute to development of testicular and cord structures as well as to development of the scrotum.

In using the hormone, it is important to give an amount large enough to insure descent of the testes in the absence of complications. The complications usually responsible for failure of adequate hormone therapy are of two types. One is congenital anomalies, such as agenesis or rudimentary tissue, which explain most clinically impalpable testes, and short cords. The other, and more common type

TABLE 1. *Scrotal route responsible for paternity in 15 men with bilateral undescended testes*

Route to Scrotum	Case	Levels of Arrest and Age Testes Reached Scrotum				No. Children	Reason for Infertility of Mate
		Right		Left			
		Position*	Age	Position*	Age		
Bilateral Spontaneous Descent	1	External ring	9	Impalpable	9	1	
	2	Impalpable	10	Impalpable	10	3	
	3	External ring	12	External ring	10	4	
	4	External ring	12	Impalpable	12	2	
	5	External ring	12	Canal	18	3	
	6	Canal	13	Canal	15	2	
Unilateral Spontaneous Descent	7	Impalpable	11	—	—	3	Left canalicular testis removed at 23, before marriage.
	8	Impalpable	14	—	—	8	Left agenesis. Exploration at 14.
Bilateral One Stage Orchiopexy	9	Canal	10	Abdomen*	10	2	
	10	Canal	11	External ring	11	2	
	11	External ring	11	Canal	11	1	
	12	External ring	12	External ring	12	3	
Unilateral One Stage Orchiopexy	13	External ring	8	—	—	4	Left testis descended from external ring at 21 and was atrophied
Spontaneous Descent plus One Stage Orchiopexy	14	External ring—Descended	8	Canal—Orchiopexy	8	1	
Undescended when son born at age 41	15	Canal—Orchiopexy	53	Abdomen*—Orchiectomy	53	1	

* Level of arrest was determined on clinical examination or at operation. The 2 abdominal testes were not palpable clinically.

of complication, is mechanical obstruction. This may be partial or complete closure of the external inguinal ring or abnormal attachment of the external spermatic fascia. The abnormal attachment of this fascia causes deviation of the testes to ectopic positions, such as the superficial inguinal pouch or, less frequently, the pubopenile area, perineum, or femoral region.

From my experience, an adequate amount of hormone is 4,000 international units of chorionic gonadotrophin (Ayerst) 3 times a week up to 40,000 units.

In this amount, under careful observation, the hormone can be given even to a young child without danger of untoward effects. Nevertheless, there is no need to give the hormone until the child is at least 5 years old because up to this age the retained testes are like their scrotal counterparts. And its use can be delayed even longer in the child with unilateral retention. But it must not be given later than puberty, as established by the appearance of the first pubic hair.

I prefer to give the hormone between age 8 and puberty. If it fails to bring the testes to the scrotum, I would do an exploratory operation or orchiopexy soon thereafter. At this age the tissues are better developed than they are at age 5 or younger, and there is thus less danger of injury to the blood supply. But surgical intervention, like hormone therapy, must not be delayed beyond puberty.

There appears to be no danger to fertility if the testes are out of the scrotum until puberty, despite histologic evidence of retarded testicular growth after age 5. In support of this observation are 14 men in my series who fathered children after bilateral retention which was not corrected, on one or both sides, before age 8. A fifteenth man had a son at age 41, when both testes were out of the scrotum. Table 1 shows how the fertile testes of these men reached the scrotum, at what age, the probable reason for infertility of the mate in 3 men, and the number of children the respective men had at followup. Only 2 of the 15 patients had had hormone therapy—1 having received 10,000 units and the other 12,000 units, which would by today's standards be considered inadequate. Each subsequently had bilateral orchiopexies at ages 10 and 12, respectively.

The best showing was among the men who had had delayed spontaneous descent. Eight were married at followup, and all 8 had children—6 after bilateral and 2 after unilateral descent, as explained in the table. In contrast, of 9 married men who had had orchiopexies, 5 fathered children—1 after a unilateral and 4 after bilateral operations, all one-stage, as shown in the table.

It is argued that delayed spontaneous descent is not representative of the typical undescended testis. Yet the testis that descends spontaneously after birth is retained outside the scrotum as long as the one brought down by orchiopexy. And it is, accordingly, subject to the same factors responsible for retarded growth and ultimately degeneration.

The superior paternity performance of patients who had had delayed spontaneous descent may be due to the fact that their testes were intrinsically better than those brought down by orchiopexy. It would seem, therefore, that while retention, if continued long enough, will contribute to infertility, in some patients the length of retention is not so much at fault as defectiveness of the testis itself. This can be absence of spermatogonia or diminution in their number, persistence of immature tubules, a blocked tubular system, or an impaired enzyme system. It may be, also, that operative trauma is a factor in infertility.

The incidence of hernia with undescended testes varies in reported series. This is probably due to the fact that while the open vaginal process in most undescended testes makes hernia a potentiality, the hernia is not always apparent clinically. In a few instances of undescended testis in adults, I have observed

that the sac was completely obliterated. And in a recent series of 44 testes that had descended spontaneously, at ages 7 to 21, there were no concomitant hernias. However, hernias developed after the descent of 4 testes. The intervals between descent and detection of the hernias were 6 months, 6 months, 2 years and 10 years, respectively.

There is no clear understanding as to how much residence outside the scrotum contributes to development of malignancy and whether orchiopexy prevents subsequent tumor formation. Among 199 undescended testes I studied, there were 4 instances of tumor, and a fifth tumor developed in one of the testes after the study was reported. The fifth tumor occurred 6 years after orchiopexy, which had been done at age 39, when the opposite testis of this man was removed for seminoma. This 1 case suggests that orchiopexy does not prevent malignancy. But it should be noted the patient was 39 years old at the time of the orchiopexy.

In The Portland Clinic there were 26 additional patients who had cancer in 28 scrotal testes. On the basis of 33 malignant testes, the percentage of cancer in undescended testes in this clinic is 15.2. On the basis of 199 clinically retained testes the percentage is 2.5.

SUMMARY

The basic principles of orchiopexy are: 1) dilatation of the scrotum for reception of the testis; 2) attainment of maximum length of the cord so that the testis can be positioned without tension; 3) high ligation of the vaginal process; 4) use of some means of fixation and traction so that the testis will remain in the scrotum.

A one-stage orchiopexy is preferable to the two-stage procedures.

Hormone therapy is indicated when testes are not palpable or when they are palpated in the canals or at the external rings. The amount used must be adequate to insure descent in the absence of mechanical obstruction or congenital anomalies. Even in the child with bilateral undescended testes the hormone need not be given before the age of 5. It can be given later if there is unilateral retention. The ideal age is between 8 and puberty. But its use should not be deferred beyond puberty, as established by the first pubic hair.

If adequate hormone stimulation does not effect descent, surgical intervention is necessary. This should be carried out soon after hormone therapy has been given, but it can be deferred until puberty without danger to fertility. It must not be deferred longer. In a series recently reported, 14 men fathered children after bilateral retention which was not corrected until puberty. And a fifteenth man fathered a son at age 41, when neither testis was in the scrotum.

Orchiopexy does not appear to prevent development of malignancy in the testes.

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DISCUSSION

DR. JOHN A. TAYLOR (New York, N. Y.): I was very much interested in this discussion, and I bow before the scientific part of it.

However, I have been interested in undescended testicles for years, having been on a service devoted exclusively to hernias in New York, where I worked mostly with general surgeons. I was working there when hormonal therapy was introduced. From clinical observations, we postulated a theory that all undescended testicles in the inguinal canal are ectopic, and that all undescended testicles in the inguinal canal have hernias, sometimes like wet tissue paper, and if one dissects carefully, a hernia can be found.

Now, if that be true, there's not much place for hormonal therapy, and I know Dr. Deming said that the number of cases in which hormones are given is small.

I also know the dictum that anyone who makes a positive statement is usually wrong, and the statement I want to make is that we hardly ever—not never—saw an undescended testicle in the inguinal canal that was not ectopic and that did not have a congenital hernia. I think that is an argument for surgery.

DR. FRANCO BIANCHI (Italy): I am very sorry for my bad English. I hope you will forgive me.

I would like to emphasize this method of orchiopexy that I think you saw illustrated in an exhibit at the recent meeting of the American Urological Association in Boston. This method is well known in Italy, because, many years ago, the technique was developed with wonderful results. The reason is that you can gain much with these methods and you can put the testicle down much better.

I do not have my record here, and I don't know how many cases I have done, but I think it was about 25, unilateral, bilateral, abdominal and inguinal. In almost all really wonderful results were obtained. It is a little longer because you must go a little higher than in the other methods.

DR. ROBERT S. HOTCHKISS (New York, N. Y.): In 1948, Dr. R. G. Harrison and Dr. A. E. Barclay experimented with interrupting the testicular artery in rats by placing sutures into the tunica albuginea. It was found that the size of the testis decreased by one third. This was explained by the fact that the main artery courses over the surface of the testes before sending branches into the parenchyma. This anatomical fact deserves consideration in the selection of operations for cryptorchism. The Torek operation involves suturing of the tunica albuginea to the fascia lata. It is possible that this interferes with the arterial supply to the testes, and causes atrophy and poor spermatogenesis. This contention is supported by the poorer results in terms of sperm production following the Torek operation as compared with those operations which employ no lateral sutures in the testes.

I would like to present the proposition that ultimately the proof for the optimal age for operation rests on a long term followup of patients after they reach their post-pubertal years. Dr. Hand's results and those of Dr. Gross indicate that over three-fourths of the patients with bilateral undescended testes who are operated upon at about the time of the onset of puberty have adequate spermato-

genesis. The proponents of early operation for cryptorchism have not, as yet, presented any evidence that a larger proportion of patients with bilateral cryptorchism have adequate fertility when they reach adulthood, if operated upon early in childhood. Until that time when such information is at hand I feel that we are not neglectful if surgery is done in the ninth or tenth year when the testes are of larger size and surgical manipulation is easier and less traumatic.

Dr. Howard I. Suby (Boston, Mass.): I just want to ask the statisticians what percentage of the undescended testes in boys of five will be in the scrotum at the age of nine if unoperated, and what percentage will be in the scrotum at puberty.

President Heckel: To whom did you address that remark?

Dr. Suby: Dr. Hand.

Dr. Meredith F. Campbell (Miami, Fla.): I have been tremendously interested in this subject for quite a long time and believe the 25 per cent of cases that Doctor Deming feels are suitable for hormonal therapy fall in the group without hernias.

You know, as has been emphasized by Dr. Taylor, there are many who believe the incidence of congenital hernia is up to 100 per cent; in my experience it is about 85 per cent, and we feel that if the patient has a demonstrable hernia at first examination he is not a candidate solely for hormonal therapy but primarily is a surgical case.

At the present time I use up to 10,000 units of choriogonadotropic hormone in a 10-day period, giving 2000 units every other day for four or five doses, and if there is unsatisfactory mobilization of the testicle, the patient is subjected to operation. That is for patients without demonstrable hernia. We also feel there is no object in waiting until the patient is past puberty to begin treatment especially since one can anticipate by gonadotropic therapeutic test (even at two years) what is going to happen at puberty.

I am aware that Dr. Hand has a remarkable series of patients with fertility after operation; Gross's figures run the same. I do not recollect what percentage of Dr. Hand's cases had the followup fertility study, but in Gross's cases it was less than 10 per cent of the total; I wonder whether the other 90 per cent would show the same high incidence of fertility.

In bilateral cryptorchism I like to start treatment before the age of five when definitive maturation of the testis begins. The extremely high incidence of failure of urogenital union is utterly amazing. So often there is stricture along the vas or particularly at its lower end with a hypoplastic testicle. About 90 per cent have a greatly elongated mesorchium which predisposes to torsion of the testis. A surprising number have complete absence of continuity of the spermatic transporting system. In short, nearly all of these imperfectly descended testes are subnormal or abnormal to start with.

Dr. John E. Dees (Durham, N. C.): I would like to ask Dr. Deming what percentage of true intra-abdominal testes that have never been in the canal he has been able to bring down by operation.

Dr. Deming (New Haven, Conn.): We have not had any technical difficulty,

and have transplanted all of them following hormonal therapy, Dr. Dees, except the 2 cases that came down. All the rest of them were readily transplanted after therapy. These were all done before puberty. Does that answer your question?

I would like to state that in this study, I have a feeling that no one has yet proved that an aspermatogenic testicle has been made spermatogenic by its transfer into the scrotum, either by hormonal therapy or by surgery.

It seems to me, when we talk about transferring the testis to the scrotum, I see only two reasons for doing it. One is to satisfy the mother, and the second is to make your patient look a little more dressy.

DR. HAND (Portland, Ore.): I should like to tell Dr. Deming that the problems I talked about concerned men who had had bilateral retention. In one patient who fathered children both testes descended spontaneously from the canals. Another patient who fathered children had bilateral clinically impalpable testes which descended from the canals or from either side of the abdomen.

Dr. Suby asked how many of the 44 testes that descended spontaneously reached the scrotum at puberty. Thirty-seven were in the scrotum by age 12.

DR. FRANK HINMAN, JR. (San Francisco, Calif.): The only thing I would like to say is, obviously we are divided into two camps, or more, and that's a very healthy state of affairs. Dr. Hotchkiss is absolutely right that it is only after years of study in series such as Dr. Hand collected that we will be able to give the answer.

However, there's a practical aspect to this. We as a group, or even as individuals, must have some program. Primarily, the pediatricians see these patients first. We need to present some sort of plan to the pediatricians, so that the children don't wander in at 12, 13, 14 years, or later, when the testes haven't descended, but that they do get to us by at least the time the first pubic hair appears, since we can use that as an end point.

THE POTENTIAL USE OF VIBRATION FOR THE DISINTEGRATION OF CALCULI*

HOWARD I. SUBY

From the Massachusetts General Hospital, Boston, Mass.

Interest and experimentation for many years in the disintegration of urinary calculi have pointed up the fact that both the physical and chemical nature of the calculus are of great importance. Physical and chemical methods for the disintegration of calculi, likewise, have both had their place in calculus therapy. We have noted for many years that stones of essentially the same chemical composition have varied in their susceptibility to dissolution. Their physical characteristics differed. Some stones were hard and some stones were soft, and the amount of interface varied. Stones that formed rapidly, however, were usually soft and tended to dissolve rapidly in proper solutions. Fragmentation of urinary calculi *in vitro* with its increasing surface production always has increased the speed of dissolution. The surface area of a cube can be doubled if the cube is broken into eight cubes, and quadrupled if the cube is broken into 64 cubes. The smaller the pieces the more grams of stone per minute can be dissolved.

Fragmentation of calculi is far from new. Many of our oldest surgical instruments have been designed to accomplish this very phenomenon, and thus in certain selected cases spare the patient from open surgery. The various lithotrites, dependent on the personal factor of the operator, have done and are doing a good job.

Vibration for the disintegration of stones or hard objects has long been a popular engineering maneuver. The jack hammer used in wrecking is a typical example. The same principle is used in orthopedic surgery with the cast cutter. The efficiency, however, of the cast cutter and jackhammer is based upon 1) the relative vibratory effect and the strength of the tool, and 2) the relative stability of the doomed product. The back and forth vibration of the cast cutter head on the hard and immobile plaster cast causes the plaster of Paris to disintegrate, whereas the soft tissue underneath which is not rigidly firm or fixed is relatively unaffected. Writing on glass has utilized this same principle. The use of this same principle for the disintegration of calculi seemed worthy of consideration, and in 1946 some interest and work in this direction were started.

A consideration of vibration naturally entailed at the outset a consideration of frequencies. The energizing vibration to be harnessed for experimentation could, depending on frequency, be:

1) *Sonic* in the audible range below fifteen thousand cycles per second with a relatively low coefficient of disintegration, but with a relatively small heat problem and with relative safety, or

2) *Ultrasonic* in the inaudible range of fifteen thousand cycles per second (15 Kc) and up. Frequencies as high as five hundred million cycles per second have been

* Engineering and technical assistance from the Raytheon Manufacturing Co.

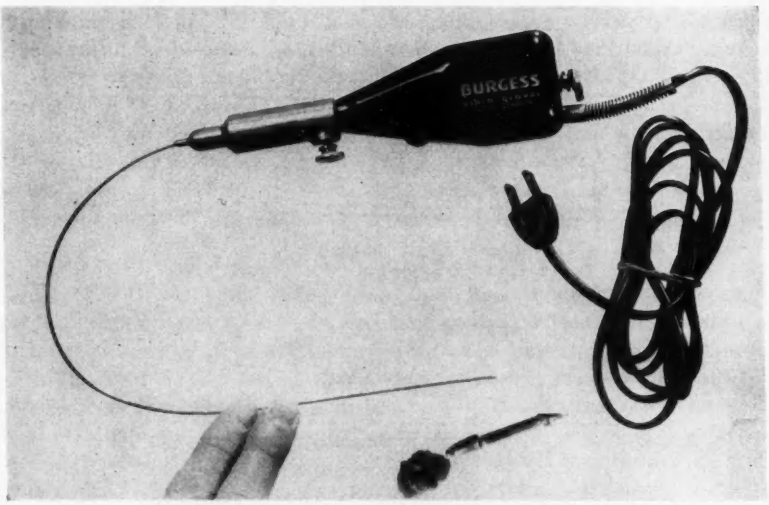

FIG. 1. Working element with modified radon seed implanter and tip

developed experimentally (Karlin, B.: Ultrasonics. New York: McGraw-Hill & Co., 1949). Energizing forces in this range have a relatively high coefficient of disintegration but generate considerable heat which creates a difficult safety problem. Ultrasonics have proved their efficiency in industry, as in machine tool and die production, the coagulation of mine dust, and in many other diversified practical fields.

Envisioning the usefulness of such a vibrating tool for impacted prostatic or bladder calculi in diverticula or even possibly for impacted ureteral calculi, an instrument was devised in November 1946 utilizing a glass writer. The working element was made by the Burgess Vibro-Crafters Incorporated of Grayslake, Illinois, and vibrated in the sonic range of thirty-six hundred strokes per minute. The problem of transmitting this force to a remote object was partially answered by utilizing a modified radon seed implanter—a coiled wire sheath with a Monel wire obturator (fig. 1). A triangular cone-shaped steel head was used on our original instrument as the cutting tool. Holding any type of calculus in one's hand or on a firm surface, it became simple to fragment it quickly and completely by exposing the piece, then pieces of stone to the vibrating tool. No pain nor evidence of soft tissue damage could be noted on the hand. The instrument seemed to have merit; it did not cause undue heat, and it performed well *in vitro*. With the absence of heat in the sonic range a sheath was not completely necessary. The friction between an obturator and the sheath obviously did influence the efficiency of the cutting tool, but it did protect the ureter from heat in cases where higher frequencies were used (fig. 2).

Following these preliminary experiments attempts were made to disintegrate urinary calculi (calcium oxalate) which had been placed in autopsy specimens.

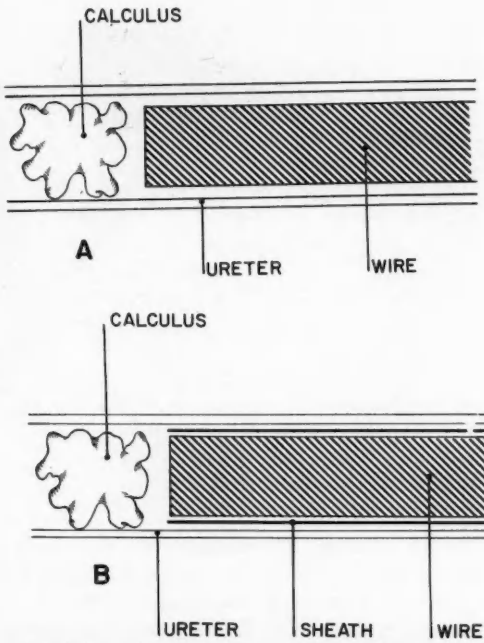

FIG. 2. *A*, no sheath in sonic range. *B*, sheath for insulation with high frequency

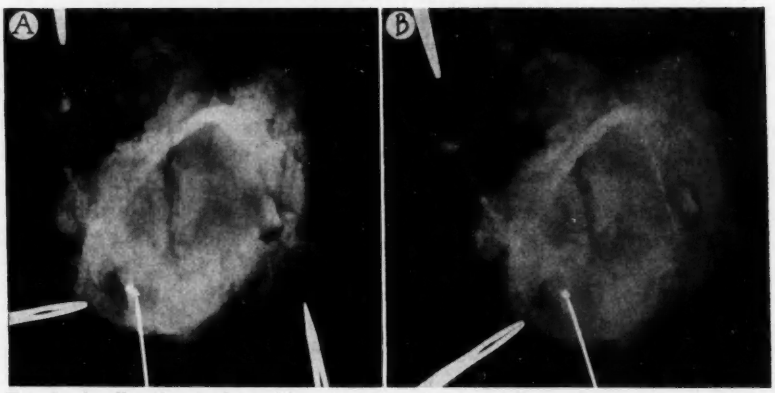

FIG. 3. *A*, vibrating tool touching stone in autopsy specimen. *B*, after 3 minutes sonic low frequency vibration.

Actual urinary stones had been placed in the lower third of the ureter and our vibrating tool was passed up to a point contacting the stones. It was at this juncture that part of our shortcomings and potential difficulties became apparent. Our vibrator was working well, but the efficiency of the experiment was far below that of the *in vitro* experiments when the stone was held rigidly. Flesh is

soft and malleable, and the stone with the surrounding ureter were all vibrating together with the working-nose of the instrument with but very little fragmentation taking place. If the stone was not slowly pushed up the ureter, or if the instrument did not bypass the stone, some good effect was obtained, but this effect was of poor efficiency. Figure 3 is a roentgenogram of an autopsy specimen with the vibrator in contact with a calcium oxalate ureteral stone. This stone was completely fragmented by manipulation for three or four minutes.

This sonic vibrating instrument was first used on a patient on October 16, 1947.

CASE REPORT

W.C., M.G.H. No. 1816, a 48-year-old man, had an external urethrotomy in 1932 for a urethral stricture. Since that time he had had recurrent prostatic and bladder calculi, with calculi in diverticula. He was admitted to the Massachusetts General Hospital on October 10, 1947 and on October 15 many of the stones were removed from the bladder. Several, however, in diverticula were inaccessible, and it was believed that these might be disintegrated with our new tool. On October 16, 1947 these stones (fig. 4) were disintegrated by vibration.

Subsequent use of this instrument on low ureteral stones seemed to indicate that this frequency tended merely to push the stone back up the ureter, or to vibrate the stone with the surrounding tissues. The potential of the instrument still remained very questionable, and in early 1947 the help of Dr. Fay of the Massachusetts Institute of Technology was solicited. Inquiry into the potential of ultrasonic vibration was made, but most of the experts seemed to think (and it later became verified) that heat could become a really difficult problem. In some rather crude experiments I was never thoroughly impressed that the increase in frequency gave enough more fragmentation to justify the heat, but these experiments were never carried out to the point of proof at that time.

Further work is now being carried out at the Raytheon Manufacturing Company. Whereas the most ideal goal to seek might be the disintegration of calculi

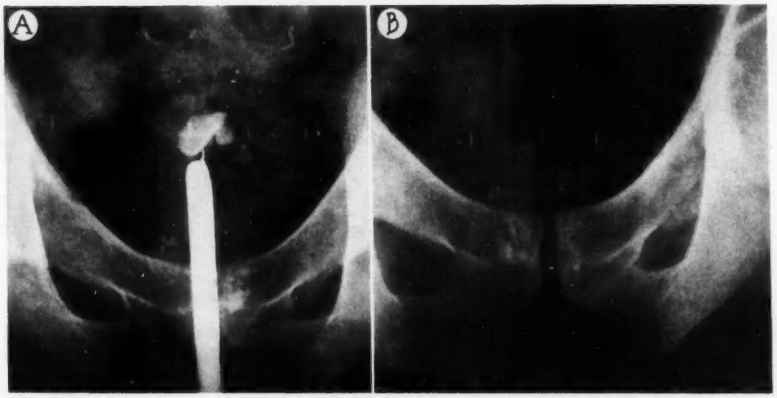

FIG. 4. *A*, vibrating tool through cystoscope in contact with stone. *B*, after disintegration by vibrating tool.

by extremely high frequencies transmitted to the stone through the urine or some other liquid introduced into the urinary tract, or directly through the surrounding soft tissues, it has seemed to me that we might probably have more immediate "potential" using lower frequencies until we have learned more about tissue damage. Ultrasonic vibration can be produced by several methods—electrical excitation of barium titanate, quartz crystals, and certain other metals. We have used the method employing an electrically excited nickel stack. Each nickel plate is separated from the next plate by a coat of nickel oxide, and vibration occurs outward from the center to a nodal point. This vibration is transmitted through a tool cone, and a Monel wire on the tool cone acts as the test-cutting tool. Selection of the transmitting wire is of considerable importance, as it is imperative to get a substance that is somewhat malleable but that cannot be compressed too much by any form of stress. We have utilized both tungsten and Monel wires, single or multiple, for this purpose. For our basic engineer-experiments we have used single Monel wires. Construction of the drill head is also of great importance. We have used square, round, and pointed types, solid and hollow. Lamport and Newman have felt that a hollow type of drill head is

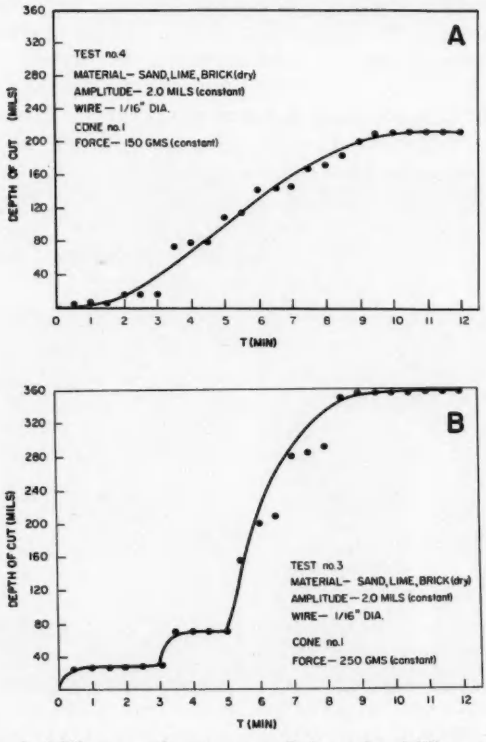

FIG. 5. *A*, smooth drilling experiment curve. *B*, irregular drilling experiment curve

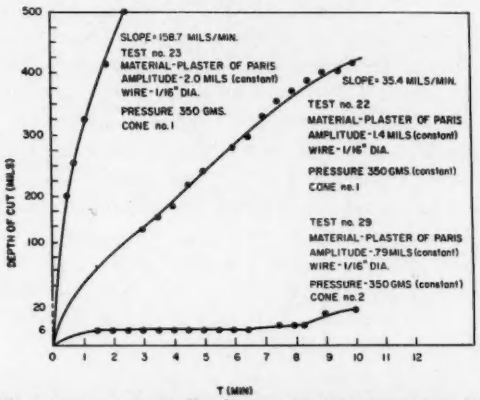

FIG. 6. Effect of varying amplitudes at constant frequency (25,000 CPS)

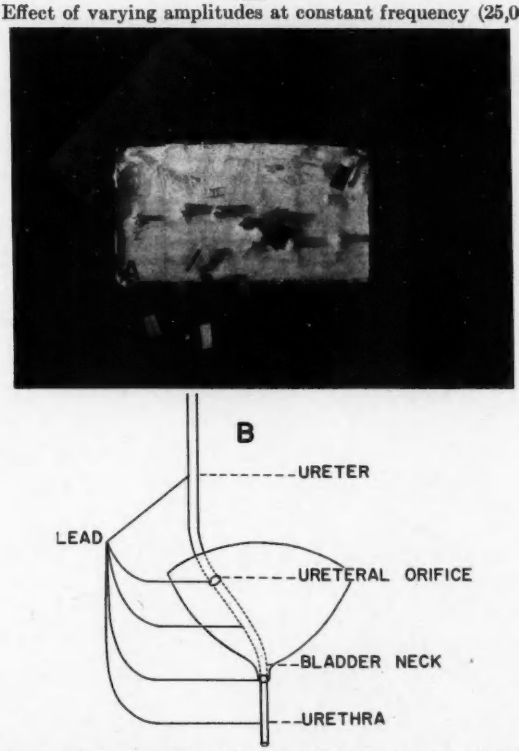

FIG. 7. *A*, plaster of Paris mold with imbedded angulated sheath. *B*, diagrammatic drawing of leads from sheath to thermocouple.

much more efficient than a solid drill head, and that it tends to avoid veering off the stone.

Attempts have been made to procure a substance whose consistency approximates that of a calculus so that carefully controlled experiments to determine the

efficiency of different pressures at fixed frequencies, different frequencies at constant pressure, and different amplitudes at fixed frequencies can be done. We have used plaster of Paris, but it has not seemed to have the same physical properties as the average urinary stone. A form of fire-brick has recently been used. This "standard" brick has been divided into small parts and used for experimentation. Mr. Harvey Miller, Mr. George Miller, and Mr. Dieter Goetze of the Raytheon Manufacturing Company Research Division have conducted engineering experiments on these substances and on stones. As in all experimentation our results have been variable and our curves not constant nor smooth. Some drillings may be perfectly smooth, whereas at other times the tool head may drill smoothly for a short time, then stop (presumably at some hard spot in the target) and then resume drilling at a normal rate (fig. 5). With single results like this it becomes obvious that each experiment must be done many times before any conclusion can be rightfully drawn. Figure 6 is a summary of approximately sixty engineering experiments on plaster of Paris showing the relative efficiency of various amplitudes at a frequency of twenty-five thousand cycles per second. It has been very obvious to us that the efficiency of the frequency of forty-three thousand cycles per second is much greater than that of twenty-five thousand cycles per second and because of this it has become possible to drill a stone with very little pressure. This frequency is being tested thoroughly at the present time. It has become quite evident to me that there should be no great problem in obtaining an optimum working condition so far as drilling or fragmentation of stones is concerned. The heat problem, however, is still one of the greatest obstacles to be overcome. In a system with a working wire (or wires) inside a sheath the points of greatest heat will be at the points where the greatest angulation occurs. We are now trying to find what frequencies and amplitudes, what working wires, and what types of sheath can best help answer this big problem. To study this we have constructed a plaster of Paris model imbedded in which is a sheath to be tested, and the working wire or wires (fig. 7). This sheath is bent to conform to the exact angulations which a ureteral catheter takes from the mid cystoscope to the mid

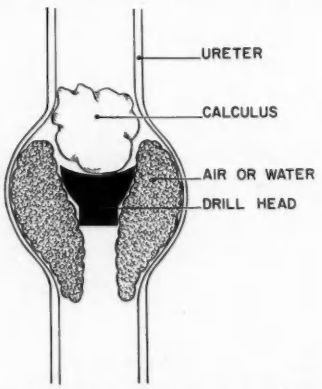

FIG. 8. Protective units separating ureter from cutting tool

ureter. Obviously the two most acute angles are near the tip of the cystoscope and at or near the ureteral orifice. Wires are connected to these strategic points of the sheath where the angulation is most acute and where it is straight and to other parts, and these wires are connected to a thermocouple and potentiometer to measure the exact heat generated at that point by the vibrating obturator. Various frequencies and amplitudes can be tried, and different types and sizes of wires, single or multiple, can replace the original wire for comparisons. The heat production seems to vary with the first power of the amplitude and with the cube of the frequency. Sheaths made from heat-resistent plastics, such as teflon, certain types of nylon, coiled wire, and ordinary woven catheters are being checked. The heat problem can be minimized by pulsing, an expression for the periodic off, on, off, on, off, on activation of the working element. There should be an optimum pulsing time and pattern for each frequency. A modified Johnson stone basket with a hollow sheath and a Monel wire obturator has seemed like a potentially useful instrument for ureteral stones too large to extract easily. The stone basket holds the calculus firmly while the obturator connected to a sonic vibrating unit disintegrates the stone. Bladder stones too hard to crush or too large to extract with the Lowsley forceps may similarly be disintegrated by vibration using an added obturator. The use of water or air-filled cushions (fig. 8) as a means of protecting the ureteral wall from the working element is now being tested, and it is felt that if proper mechanical engineering can be effectively directed to accomplish a high degree of safety, this form of therapy may have some potential use. There are many problems to be solved before the method will attain clinical importance.

SUMMARY

Experiments using sonic and ultrasonic vibration for the disintegration of calculi have been conducted. The effect of frequency, amplitude and other engineering variables has been studied. Heat production and tissue trauma are the major complicating factors which preclude the clinical use of ultrasonic vibration for calculus disintegration at the present time. Calculi in patients have been disintegrated by vibration in the sonic range. Vibration may enhance the potential of dissolution therapy. Further experimentation is being hopefully but skeptically conducted.

262 Beacon St., Boston 16, Mass.

USE OF CLORPACTIN WCS 90 FOR RELIEF OF SYMPTOMS DUE TO INTERSTITIAL CYSTITIS

WM. NILES WISHARD, JR., MYRON H. NOURSE AND J. H. O. MERTZ

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Interstitial cystitis has been the happy hunting ground of therapeutics since Hunner first described the lesion in 1915. It has been locally treated by segmental or subtotal resection, electrocoagulation, overdistention, instillation of 2 per cent silver nitrate and injection with alcohol, cortisone etc. Systemic treatment has included the following drugs: neoarsphenamine, urinary antiseptics, emetine, cortisone and probanthine. So far as I am aware no one has ever reported any predictable certain method of cure. The best that can be said is that the symptoms may be alleviated.

Overdistention and instillation of 2 per cent $AgNO_3$ has been the most acceptable method of relief in our hands until O'Conor[1] reported the use of clorpactin WCS 90 at the 1955 meeting of the North Central Section of the American Urological Association. Infected with his enthusiasm, we at once obtained a supply of the preparation from the Guardian Chemical Corporation of Long Island City, N. Y. and wish to report on our results.

Clorpactin[2] is a generic term for closely related, highly reactive chemical compositions having a modified derivative of hypochlorous acid in a *buffered* base. Its bacteriocidal potency is similar to that of elemental chlorine without the latter's toxicity or destructive effect on tissue cells. Clorpactin vapor is as effective as the solution. It is a white soluble powder which is stable in the refrigerator but should be used within a few hours after mixing with water. Two grams are dissolved in 1000 cc tepid water. Tap water may be used but we have found distilled water gives a clearer solution. The solutions are germicidal, fungicidal, viruscidal, nontoxic and nonirritating in therapeutic doses. The activity of clorpactin is dependent upon the liberation of hypochlorous acid and to its oxidizing effects, wetting and penetrating properties and detergency. The material is highly buffered, its pH 6.5. It also deodorizes. Chemically it is monooxychlorosene whose active chlorine content is about 4 per cent. The label on the box reads "active chlorine derived from calcium hypochlorite." Its phenol coefficient is 27.[3] It should be mixed in glass or ceramic containers. It will not injure stainless steel but will oxidize copper or other metal surfaces. A 0.28 per cent solution kills tetanus spores in 5 minutes. A 0.5 per cent solution in 1 minute makes tubercle bacilli harmless to guinea pigs. A 1:12000 solution kills entamoeba histolytica in 48 hours. It is bacteriocidal to common bacteria exposed for 1.5 minutes in 1:5000 dilution.[3] It will kill cultures of Staphylococcus aureus in a few

[1] O'Conor, V. J.: Clorpactin WCS 90 in the treatment of interstitial cystitis. Quarterly Bul. N. W. U. Med. School, **29:** 392, 1955.

[2] Clorpactin, Guardian Chem. Corp. pamphlet.

[3] Swanker, W. A.: Use of clorpactin WCS 90 as an antiseptic in surgery. Am. J. Surg., **90:** 44, 1955.

seconds. It has wide range antibacteriocidal action, no serious side effects and organisms do not develop resistance to it.

Clorpactin WCS 90 is used in dermatology for athlete's foot, psoriasis and acne; WCS 60 in oral and dental hygiene; WCS 90 in body cavities, wounds, bladder, renal pelvis and fistulas; XWCS in massive or deep infections; CXB in the vagina; and 2 DC for sterilization of instruments. CXW is being studied for aerosol application. The preceding are used topically.

Zwerling[4] has used clorpactin with marked improvement in the treatment of pharyngitis, globus hystericus, canker sore and oral antral fistula. Swanker[3] reports its usefulness in wet dressings on skin grafts and for prevention of stitch abcess. Lattimer[5] first used it in the bladder with beneficial results in healing tuberculous ulcers which had not responded alone to streptomycin, PAS and INH. He found that tuberculous ulcers responded in 2 weeks to the use of 0.2 per cent solution of clorpactin WCS 90 every 3 days. More frequent use caused hematuria. He recommends 60 cc instilled in the bladder 1 minute, with 5 interchanges of the solution, and found that bladder capacity increased although permanent scarring was not absorbed.

O'Conor[1] first used clorpactin WCS 90 for interstitial cystitis. He overdistended the bladder for 1 minute weekly for 4–5 weeks in chronic longstanding cases, finding that bladder capacity increased while symptoms decreased. He also believes that it would be of help in clearing up sloughing or ulcerative lesions of the bladder.

We first used clorpactin WCS 90 in October 1955, dissolving 2 gm. of the powder in 1 quart of tap water. This gives a slightly turbid solution with foam on the surface. Later we used tepid distilled water, pouring the powder on the water, and found that it dissolved faster and gave a clear solution. We have always used the solution within an hour or two after it is made up. The powder is kept in a refrigerator. Frequently the entire quart is not used and the remainder is discarded. Inasmuch as the material is somewhat expensive we have found it more economical to weigh it into half-gram and gram portions to be dissolved in 250 cc or 500 cc lots which leave less waste. A catheter is placed in the bladder to empty it. The bladder is then irrigated gently (without distention) with water, after which clorpactin is injected. In patients with a very sensitive bladder only an ounce or two is instilled for a minute. This is withdrawn, the bladder again irrigated with water, and 1 ounce of 2 per cent metycaine instilled in the bladder just before the catheter is withdrawn. In less sensitive patients the bladder is dilated to comfortable capacity with clorpactin, which is then withdrawn. Several such interchanges are used so that the solution is in contact with the bladder for 3 to 5 minutes. We have also tried more forceful overdistention in the hospital on anesthetized patients but do not find that the results differ significantly. We have followed the suggestion of O'Conor in repeating the treatments weekly for about

[4] Zwerling, M.: Clorpactin WCS 90: A new antiseptic. Arch. Otolar., **62:** 157, 1955.
[5] Lattimer, J. K. and Spirito, A. L.: Clorpactin for tuberculous cystitis. J. Urol., **73:** 1015, 1955.

5 treatments. In the hospital we have repeated treatments as often as every 4 days. After the initial course a month elapses following which another irrigation with clorpactin is given. After that we have had the patient return at such intervals as she deems necessary.

The first treatment or two is apt to be more distressing than instillation of 2 per cent $AgNO_3$. A few patients have required hot sitz baths and codeine afterward, but we have not had to make any house calls. We have had no serious untoward effect nor sensitivity. Hematuria rarely ensues. One patient had chills and fever after treatment. All had temporary aggravation of symptoms for 12–48 hours.

We have treated 20 patients by this method in the last 6 months. Eighteen of these were women. Four of the group were under 40, five between 40 and 60, eight between 60 and 80, one over 80. Fourteen were married, four were widows, one single and one divorced. Eighteen had been previously treated by other methods, varying in time from 1 to 15 years. Previous treatment had consisted of overdistention of the bladder with water, instillation of 2 per cent $AgNO_3$, urethral dilation, urinary antiseptics, light fulguration, ureterosigmoidostomy (in one case), and probanthine. Fifteen patients had had from 1 to 14 previous hospitalizations for treatment, five had had none. Ten had had previous operations, most of them pelvic. Clorpactin has been used on each patient from 1 to 10 times, with an average total of five for each.

Symptoms which required treatment were as follows: frequency in all, nocturia in most, urethral and bladder pain in many, hematuria in 2. As one patient expressed herself, she went so often she met herself coming back. Bladder capacity varied before treatment from 3 to 20 ounces. Regardless of bladder capacity all complained of small voidings. Other diseases we have found coincidentally in this group are: multiple sclerosis, cholelithiasis, epilepsy, manic depression psychosis, diverticulosis, caruncle, carcinoma of the prostate, prostatic hypertrophy, urethral stenosis, hydronephrosis, granular urethritis, vaginitis and asthma.

RESULTS

First let us dispose of the unsuccessful results. Three were not improved, one doubtful and 1 only slightly. One of the failures had previously had a ureterosigmoidostomy without relief from the operation or subsequent clorpactin. Ultimate cystectomy was done. Two of the failures were just not improved. The slightly improved patient also had multiple sclerosis. The doubtful patient also had carcinoma of the prostate and was improved by clorpactin and stilbestrol. Two patients had been treated too recently to evaluate and 1 has not been followed.

The remaining fourteen all report that subjectively they have been more relieved than by any previous method of treatment. Bladder capacity has increased. The ability to utilize the maximum bladder capacity has improved, thus lessening greatly the frequency and nocturia. In all 14 urethral burning and pain

in the bladder have become almost abolished. Hematuria has stopped. No patient has expressed any regret in the change to clorpactin. In no instance where the patient has been cystoscoped after completion of treatment have we been unable by overdistention of the bladder to demonstrate the area of interstitial cystitis, so it does not cure. It does, however, ameliorate symptoms, make life more pleasant and give us something more effective to offer in the treatment of interstitial cystitis.

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AORTIC COMPRESSION IN THE MANAGEMENT OF MASSIVE HEMORRHAGE FROM THE RENAL ARTERY AT NEPHRECTOMY: REPORT OF A CASE

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Massive and sometimes uncontrolled hemorrhage from the renal artery is a problem faced by all urologic surgeons. Its gravity is appreciated when the total renal blood flow of 1240 ml. per minute is compared with the blood volume of 4500 ml. in the normal person. According to Best and Taylor, a rapid loss of 30 per cent of the blood volume without immediate replacement is lethal. By simple calculation, it is seen that the operator has only a very short time to bring the renal artery under control in order to avoid a fatal outcome.

The most common cause of uncontrolled bleeding at nephrectomy is the retraction of the artery, especially the left, at the time of its division or when the clamps are removed with the application of ligatures. Avulsions of the renal artery from the aorta may occur in difficult mobilizations of the kidney as in the case of large renal tumors. Much less commonly, bleeding is encountered from rupture of an arteriosclerotic vessel or aneurysm of the renal artery when clamps or ligatures are applied. A rent in the vena cava is much more readily controlled.

Of the methods used for recovering a bleeding artery, the simplest and best known is to grasp immediately the vessel with the fingers. With this maneuver, the blinding flow is stopped, the wound can be evacuated of blood and blood clots, and the operator or his assistant is then given an opportunity to isolate and secure the vessel under direct vision. Indiscriminate clamping in a bleeding wound is to be condemned as both ineffectual and likely to cause injury to adjacent structures. Packing of the wound is helpful in low pressure bleeding from the renal vein or cava. The usefulness of this procedure is limited in arterial hemorrhage because of bleeding into the pack. Packing plus pressure can at times be of help in allowing the operator a brief interval to 1) organize his attack; 2) begin massive transfusion; 3) obtain, if needed, more adequate exposure; and 4) have special vascular instruments readied. The operator is then able to utilize the method described by Rathbun of insinuating the fingers beneath the pack, palpating the aorta, and by moving caudally, grasp the renal artery at its origin.

Scott and his group have described a case of massive bleeding from the right renal pedicle. Hemorrhage was temporarily controlled by a gauze pack and pressure. On the ninth postoperative day, the wound was opened and the pack slowly withdrawn. Brisk bleeding occurred as the last of the pack was removed, and attempts to secure the pedicle were unsuccessful. Therefore, the wound was repacked and closed. On the eighteenth postoperative day, the patient suddenly began to hemorrhage into the pack, and went into profound shock. The packing was reinforced and the vital signs stabilized by transfusion in preparation for surgery. A transverse abdominal incision was made and the aorta approached

through the lesser peritoneal sac. By manual compression of the aorta against the spine, bleeding was controlled. The right renal artery was identified and successfully ligated. On the thirty-fourth day after his operation, the patient left the hospital.

Recently, we have encountered a situation in which bleeding from the left renal artery could only be controlled by aortic compression. Our approach to the aorta was transthoracic. This route was selected as the simplest and quickest for the patient in the decubitus position. The following clinical report illustrates the usefulness of this maneuver.

A.G. (G-NHH 43-18-71), a 68 year-old white man, was admitted on July 28, 1955, with a 1-year history of intermittent left flank pain accompanied by chills and fever. Urologic workup disclosed calculus pyonephrosis on the left with complete loss of function and with physiologic compensatory hypertrophy in the right kidney as shown by differential phenolsulfonphthalein excretion. On the following day, the left kidney was approached through the left flank, resecting the twelfth rib. Endotracheal anesthesia was used. The perirenal fat was indurated and adherent to the kidney. Exposure of the pedicle following division of the ureter was tedious, owing to extensive acute and chronic inflammatory reaction. When the pedicle was free, a No. 2 chromic ligature was applied proximally, followed by application of three large Kelly clamps. The pedicle was then transected between the second and third distal clamps and the kidney removed. A suture ligature of No. 2 chromic catgut was next placed through the pedicle. As the ligature was being tied, even before the proximal clamp was loosened, there was a sudden gush of arterial blood into the wound. The operator could neither feel the bleeding vessel nor evacuate blood from the wound quickly enough with the aspirator to visualize the point of hemorrhage. The wound was then tightly packed, blood was ordered from the blood bank, an additional vein was cannulated, and massive transfusion was begun under pressure. Despite the packing, the patient's blood pressure fell instantly to shock levels. Two thousand cubic centimeters of whole blood rapidly administered failed to raise the blood pressure above 80 mm. of Hg systolic. A second attempt was made to locate the bleeding vessel, but this was thwarted by the rapid welling up of blood in the wound.

The patient's blood pressure continued to fall. Within a few moments the systolic pressure and pulse were unobtainable. The patient's condition was desperate. As repeated efforts to control hemorrhage through the flank had failed, it was decided to isolate and occlude the aorta above the renal artery in an area uninvolved in the dense perinephric phlegmon. Dr. W. W. L. Glenn, chief of the cardiovascular section, was called and participated in gaining control of the bleeding renal artery. He suggested that a transthoracic approach for compression of the aorta would be best. Rather hastily, the incision was extended superiorly, the eleventh rib resected, and the pleura opened. The aorta was identified by palpation and was slowly occluded by digital pressure. Almost instantly, the brachial blood pressure rose, thus, at least temporarily, insuring cerebral oxygenation.

The flank packing was slowly removed. Gently the wound was evacuated of

blood and clot. Bleeding had stopped completely. Then, as the tension was eased on the aorta, the operator was able to visualize and identify the renal artery. It was apparent that the severely atheromatous vessel had been severed in tying the ligature. An atraumatic, fabric-shod Crawford clamp was placed on the proximal portion of the artery while the distal end was oversewn with two layers of 5-0 arterial silk, care being taken to avoid further injury to the vessel. The renal vein was next secured with two No. 00 chromic ligatures and its clamps were removed. Following the closure of the artery and continuation of the transfusion to 3000 cc, the patient's blood pressure returned to normal levels. The incision was carefully closed in layers and the pleural cavity was drained with tube suction for 48 hours.

The patient was discharged on the fourteenth postoperative day with wound completely healed. The renal function showed 40 per cent output of phenolsulfonphthalein in 2 hours, the nonprotein nitrogen was 39, and the x-ray disclosed normal roentgenogram of the chest.

SUMMARY

A technique is described by which massive bleeding from the left renal artery was controlled by immediate manual compression of the thoracic aorta. The transthoracic approach for compression of the aorta is both rapid and easy, thus enabling the early recovery of the bleeding vessel and its ligation, and preventing an operative mortality. In addition, it does not prolong the patient's hospitalization. Furthermore, the utilization of the services of the vascular surgeon or his special instruments can prove of inestimable value to our specialty.

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DISCUSSION

Dr. John K. Lattimer (New York, N. Y.): We, too, are working with ultrasound along much the same lines as Dr. Suby. At this moment we are working with Dr. Harold Lamport, whose report* you heard at the recent Boston meeting of the American Urological Association. We are devoting our efforts just now to animal experimentation. In dogs, we are reproducing the expected conditions of the use of the instrument in humans and trying to be absolutely sure that neither the ultrasound nor the idiosyncracies of the instrument might be harmful to the soft tissues. It is perfectly obvious that when you impact a stone in the ureter in such a way that you can not get by it by ordinary methods, that the ureteral wall may become edematous and fragile.

The apparatus you have seen. I think our machinery is essentially the same as Dr. Suby's. It does seem to us important that we, as urologists, should keep abreast of any possible new developments that might help in our specialty.

Now, in regard to the use of clorpactin, we have found it helpful in cleansing tuberculous ulcers of the bladder. It is fairly irritating for routine use in ordinary cystitis, and is not so effective as 10 per cent formalin for sterilizing cystoscopes. As. Dr. Wishard said, it is similar to clorox, and it is effective as a detergent. It is very effective in cleansing wounds, just as Dakin's solution is.

At the same time, it has no magical properties. We have been impressed, the same as Dr. O'Conor and Dr. Wishard, that it is helpful in conditions such as interstitial cystitis, but by no means does it cure them.

Dr. Vincent J. O'Conor (Chicago, Ill.): I'd like to precede my remarks by assuring this group that I neither own stock in the Guardian Chemical Company nor do I get a commission on the sales of clorpactin.

I think many of you were present at Pebble Beach last year when John Lattimer spoke—and also at Los Angeles, I think—in regard to the encouraging results that he had had in using clorpactin as an irrigating medium in resistant cases of tuberculosis of the bladder, and his enthusiasm spilled over on me, and I immediately, on my return from that meeting, got in touch with the people that make this and got a supply of it to try out.

We had two or three cases of tuberculosis of the bladder that were not doing very well after nephrectomy from the bladder capacity point of view, and one day one of my 22-year-old interstitial cystitis patients came in, and I said to the office nurse, "Let's try this stuff on this woman. We've tried everything else. She's gone from one urologist to the other. We have had her in the hospital a dozen times. Maybe clorpactin might do something for her."

So that was the start in using it in interstitial cystitis.

Now, I have no rationale to offer for using it in interstitial cystitis. In the first place, I don't know what causes interstitial cystitis. In the second place, I do know that interstitial cystitis in the realm of our present understanding is not a

* J. Urol., **76:** 520, 1956.

bacterial disease, so that in using clorpactin in the treatment of interstitial cystitis, we are not using it to kill any bacterial organisms.

When the North Central Branch met in Chicago, we had these three-minute sessions, and I got up and told of our experiences in the treatment of interstitial cystitis with clorpactin, and gave an optimistic report. Since that time, I have been sorry, not from the point of view of the recommendation, but from the point of view of the work that it has caused me that I didn't keep it to myself, because I have had more letters and more correspondence and more people writing me about this thing than over any other work I have ever done.

I was criticized by some people who don't listen to what you tell them, because I didn't say in my original talk before the North Central Branch that the patients would get worse before they got better. I emphasized that very distinctly, that the first couple or three or four treatments might make them much more uncomfortable than they were before the treatments started. It doesn't always, but it's a distinct possibility.

Naturally, if you make a patient worse with the treatment, the patient may refuse to go on with the treatment unless he or she has enough confidence in you to believe that you are on the right track and that you eventually will help, and many of the gripes that have come from the use of clorpactin, I think, have resulted from the fact that after a couple of treatments, or three, the patients have complained about not feeling as well as they did before, and the doctor has quit using it.

Now, the criterion of improvement in interstitial cystitis, in my opinion, rests on two things. It rests first of all upon the patient's sense of well-being, and the sense of well-being is a rather broad statement in the case of interstitial cystitis, because these patients do not only have pain in their bladders and urethras, but the chronic ones that are intractable have a distinct feeling of being below par in general. You have all experienced that. These patients—you're almost willing to put them in the neurotic class after you have tried to treat them for a while.

The second criterion of improvement, of course, is the bladder capacity and how long they can go between urinations.

Clorpactin used as we have used it has been almost universally helpful in improving these patients. We have selected only the intractable patients in our practice for use with clorpactin. The people who have done well on the ordinary measures, like overdistention with weak solutions of silver nitrate, or even the instillation treatment of silver nitrate and local anesthesia—we have not used clorpactin on them. We have selected only the patients who have not done well on other methods of treatment, and I can say very honestly that we have never had as much gratification on the part of people whom we used to hate to see come in our office as we have with this treatment.

Now, I want to re-emphasize that you must tell the patients that this is an irritating form of treatment, that they will probably feel worse after the first two or three treatments. We prepare them by giving them sedation and explaining to them that for 48 hours, maybe 72 hours, after the treatment, they will be more unhappy than they were before they had it. If you do that, the patient

will go along with you and take further treatment. If you don't do that, the patients are liable to go to the next doctor around the corner, as they usually have done before, anyway, and you won't see them again.

Now, we have had a couple of interesting kickbacks with clorpactin. We have had 2 patients who had a chemical reaction. In other words, they had what I would call acute chemical cystitis.

Mr. Globus, who makes this stuff and who, as John Lattimer says, has gone off the deep end with it, assures me that this drug is not allergenistic. I thought with the first one of these we saw that it probably was an allergic reaction of some sort, but apparently it was not. It was a chemical reaction. A chemical reaction can happen in the course of treatment but is no reason to stop further treatment with the drug.

The thing that impresses me about this material is this. First of all, these women experience a sense of well-being that they have never experienced with any other form of treatment. Even those who have had a lesser increase in bladder capacity are very much pleased with the way they feel, as compared to before treatment, and how long we are going to have to keep this treatment up for these people, I don't know, because I have had exactly the same experience as Dr. Wishard.

A patient comes in with a bladder capacity of 60 cc and has elusive ulcers, although most of these patients don't have elusive ulcers at the time we treat them. The bladder capacity increases to 300 or 400 cc and the ulcers look just the way they did before we started the treatment.

Now, whether the elusive ulcers have the same cause as the condition or not, I don't know. I think actually our knowledge of interstitial cystitis is meager indeed, and I have grown up with it. I mean, the condition was described by Dr. Guy Hunner about the time I was a resident, so I have lived through the history of it.

I don't think we know much about it, and we only offer clorpactin as a method for making these people more comfortable and increasing their bladder capacity, and I think the important thing is that if you have a patient who reacts too violently to the first treatment of clorpactin, to dilute the solution to 1 per cent or ½ of 1 per cent, or any per cent you want, and then gradually bring it back to the usual strength, i.e., 2 per cent.

I also have had the same experience as Bill has had, that it is not the overdistention of the bladder with this material that gives us the improvement, apparently, because we have purposely taken patients whom we were overdistending under trilene anesthesia before, and simply used 60 or 70 or 100 cc of this material and held it in there, and let it run out, and put the same amount in again and let it run out, and do it four or five times, and they obtained just as much improvement as the patients that we have distended with 300 or 400 cc.

Dr. Bulkley and Dr. Sokol are going to report our experience at the Urology Section of the AMA. I haven't seen their figures yet, but I'm sure they are going to be optimistic, also, at least from a control point of view.

Dr. Fletcher H. Colby (Boston, Mass.): I don't want to unnecessarily pro-

long this discussion about clorpactin, but I would like to lay one more flower on its grave.

We're going to be faced more and more, I believe, with this problem that, with the increasing and persistent use of antibiotics we're going to see more and more fungus infections of the urinary tract. A case in point is a 65-year-old lady in Boston who, following the extensive use of antibiotics for pneumonia, had a very severe and persistent fungus infection of her bladder with Monilia albicans; I sought help from every direction, from the determatologists, Vincent O'Conor, and everybody else, as to what to do about it.

Nothing that we tried had any appreciable effect on her fungus infection except mycostatin, which was used locally in her bladder and did quiet down her very severe hemorrhagic cystitis. Then clorpactin came along, and that was the answer to a maiden's prayer, I thought.

So, we put the old lady on irrigations with clorpactin, at first every three days, and then, finally, every other day, and clorpactin failed completely to eliminate this severe infection.

Dr. John K. Ormond (Pontiac, Mich.): Just a question to Dr. Deming. Is the aorta as easily gotten at on the right side as the left, or would you have to go through the left side of the thorax even if you were dealing with the right kidney?

Dr. Howard I. Suby (Boston, Mass.): I would just like to say that we will continue to work along with Dr. John Lattimer to see if we can get an accurate answer to this problem. I'm sure that the problem will be pursued with some optimism but with a large amount of skepticism.

Dr. W. N. Wishard (Indianapolis, Ind.): I just wanted to reply to Dr. Lattimer that the claims that I was making were not mine for the bacteria-killing effects of clorpactin. It was impossible for me, in reading my paper, to cite references, but those claims, as he knows, came from the pamphlet that is published by Guardian Chemical Company.

We have been using it for a lot of other infected cases with some good results. I might mention the last use that I have found for it. My office nurse told me that it cured poison ivy. She had poison ivy, and nothing else worked, and she didn't know what to do, so she tried that and it worked.

Dr. O'Conor: It's the greatest thing in the world for athlete's foot!

Dr. Clyde L. Deming (New Haven, Conn.): It's not as easy to go through the right side, but the surgeon could go through the abdomen and reach the aorta readily.

I dislike to report a single case, but I'm sure that we need at times all the methods we can possibly bring to focus in cases of distress, and I feel that if you have trouble on the left side that the transthoracic approach will answer your purpose readily and be successful.

PREOPERATIVE DIFFERENTIATION BETWEEN HYPERPLASIA AND TUMOR IN CUSHING'S SYNDROME

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The identification of the cause of Cushing's syndrome (hyperplasia, adenoma, or tumor) before operation allows a more direct surgical approach and permits the reasoned use of excision and hormones. Our experience in 20 patients who came to surgery is reviewed for the value of hormonal stimulation and suppression tests and of x-ray procedures for differentiation between hyperplasia and tumor.

THEORETIC CONSIDERATIONS

Overactivity of the adrenal gland may cause androgenic and anabolic changes (the so-called adrenogenital syndrome, and virilization) if the principal products are androgenic hormones, reflected in the excretion of urinary 17-ketosteroids (fig. 1). On the other hand, the secretion may have an almost pure catabolic or nitrogen-wasting effect, resulting in the increased excretion of 17-hydroxycorticoids (Porter-Silber chromogens). Ordinarily, a mixture of anabolic and catabolic effects is found. The tests of hormonal secretion assess approximately this relative increase of androgens and of corticoids.

The excretion of anabolic-androgenic and catabolic hormones not only differentiates virilization from Cushing's syndrome, but also allows to some extent for the distinction between adrenal hyperplasia, adenoma, and carcinoma. Roentgenography allows further distinction between hyperplasia on the one hand and adenoma and carcinoma on the other.

The relative usefulness of these distinct approaches, hormonal excretion and x-ray signs, was evaluated in a series of 36 cases of Cushing's syndrome which have been studied at the University of California Medical Center, San Francisco, since 1952, at which time urinary 17-hydroxycorticoid excretion studies were first set up. Twenty of these patients have come to operation and form the actual basis for our observations and conclusions.

HORMONAL DIFFERENTIATION

Basal hormone studies. Cushing's syndrome is suspected by clinical examination (table 1[1]), but requires substantiation by the laboratory. An elevation of the basal determinations of 17-hydroxycorticoid (hydrocortisone and cortisone) and their inactive excretion products will strongly suggest abnormal activity of the adrenal cortex.[2] A level above 12 mg./day of 17-hydroxycorticoids is suggestive, and higher levels are practically diagnostic.[3-5]

[1] Plotz, C. M., Knowlton, A. I. and Ragan, C.: The natural history of Cushing's syndrome. Am. J. Med., **13:** 597, 1952.

[2] Liddle, G. W., Island, D., Cornfield, J. and Forsham, P. H.: A clinically significant

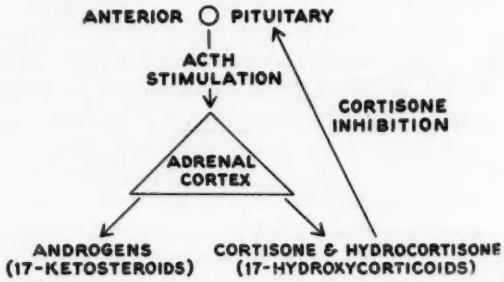

FIG. 1. Pituitary ACTH stimulation of adrenal cortex releases androgens and corticoids. Corticoids inhibit further adrenal stimulation, and so establish a balance.

Adrenal hyperplasia produced a significant increase in corticoid excretion in this series (mean level of 22 mg./day) and usually of the androgens as well (fig. 2). These levels are somewhat higher than that from adenomas (mean of 15.5 mg./day) which show a highly variable baseline characteristically. Thus two or three 24-hour collections should be obtained when in doubt. The highest basal levels were seen in 2 cases of cortical carcinoma (mean of 38.5 mg./day), and these proved to be extraordinarily stable. While the level in the individual patient may not necessarily be diagnostic because of variations from the mean which produce some overlapping, it usually is strongly suggestive.

ACTH stimulation test. Hyperplasia and adenoma, while abnormally active in hormonal secretion, are composed of essentially normal cells and so probably would remain dependent to some extent on pituitary control (fig. 1). The administration of pituitary adrenocortical stimulating hormone therefore should increase 17-hydroxycorticoid (and 17-ketosteroid) output. Carcinoma, on the other hand, its cells growing independently, would be expected to be unresponsive to ACTH stimulation.

The ACTH stimulation test has been standardized: 20 units of ACTH are given in slow intravenous drip over a period of 8 hours, and urine specimens are collected for the 24 hour period.[5] It is found that the normal adrenals showing a 3 to 5 fold increase over the baseline are rarely stimulated to excrete as much as 50 mg./day, whereas hyperplastic adrenals excrete more than this (fig. 2). The rise in 14 surgically proved cases was found to be from a mean resting level of 22 to a post-stimulation mean high of 70.6 mg./day. In 4 cases of adenoma, the rise definitely was greater (5 to 7 fold) to a mean level of 73.5 mg./day. Carcinoma produced no significant rise in corticoid excretion in our 2 cases (from 61 to 65, and from 16 to 19.5 mg./day).

Attempt at correlation between degree of rise in 17-hydroxycorticoid excretion

steroidogenic assay of corticotropin (ACTH) administered extravascularly to human subjects and to guinea pigs. Endocrinol., **55:** 575, 1954.

[3] Forsham, P. H., Kolb, F. O., Liddle, G. W. and Island, D.: Dynamics of adrenal cortical activation in different functional states. Am J. Med., **17:** 108, 1954.

[4] Forsham, P. H. and Thorn, G. W.: The adrenals. Chapter 4 in Williams, R. H., Textbook of Endocrinology. Philadelphia: W. B. Saunders Co., 1955.

[5] Laidlaw, J. C., Reddy, W. J., Jenkins, D., Abu Haydar, N., Renold, E. and Thorn, G. W.: Advances in the diagnosis of altered states of adrenocortical function. New Eng. J. Med., **253:** 747, 1955.

after ACTH stimulation and the weight of the gland(s) at operation gave an r of 0.12 (0.55 would be the 5 per cent probability level), indicating absence of correlation. However, only 14 cases were involved, and in several of these, only one gland was removed, so that total weight was estimated by doubling the weight of the single gland. That this method would not be entirely accurate is suggested by

TABLE 1. *Diagnostic and therapeutic procedures in Cushing's syndrome*

	Hyperplasia	Adenoma	Carcinoma
Signs & symptoms[1]	Obesity 97% Hypertension 84.5 Oligomenorrhea—impotence in men 78.5 Hirsutism 71 Plethoric appearance 69.5 Weakness and backache 66.5 Purple striae 65.5 Acne, skin pigmentation, or other rash 54 Mental symptoms 49 Headache 46 Ankle edema 44 Purpura or easy bruisability 41.5 Poor wound healing or severe infection 36 Polydipsia or polyuria 32 Neurologic symptoms or signs 28 Virilism 7 Exophthalmos 7	More rapid onset	Similar
Hematologic data	Less than 50/cu.mm.	Similar	Similar
a. eosinophils	Less than 15% of total WBC		
b. lymphocytes			
Skull x-ray	Hardly ever enlargement of the sella turcica. Osteoporosis with intact lamina dura	Similar	Similar
Glucose tolerance test	Diabetic curve	Similar	Similar
Hormone excretion	Moderately elevated	Slightly elevated and changing from day to day	Most elevated and fixed
a. 17 hydroxycorticoids	(Normal male 6–14 mg/24°) (Normal female 4–10 mg/24°)		
b. 17 ketosteroids	Slightly elevated (Normal male 10–20 mg/24°) (Normal female 5–15 mg/24°)	Often low	Very greatly elevated
c. 8 hr. ACTH test (20 u. ACTH I.V. over 8 hrs.)	Rise above 50 mg./day with normal 3–5 fold increase over baseline	Rise above 50 mg./day with greater than 5 fold increase over baseline	No rise

TABLE 1. *Continued*

	Hyperplasia	Adenoma	Carcinoma
d. 9-alpha fluorohydrocortisone suppression test 1 mg. 9-alpha fluorohydrocortisone acetate (Squibb) for every 3 mg of urine 17-hydroxycorticoid, given in 4 divided doses q 6° p.o. for 3 days. Urine collection on 3rd day	Hydroxycorticoids decreased 50% or more (unreliable)	No change or less than 50% suppression	No change (found rarely in fulminating bilateral hyperplasia)
Adrenal roentgenograms			
a. Plain film	Adrenals can seldom be visualized	? Left renal displacement (15% lower)	Same
b. I.V. Urogram	Adrenals can seldom be visualized	Distinguish renal masses	Same
c. Retroperitoneal oxygen insufflation (with tomograms)	*Bilateral* enlargement	Unilateral change, contralateral atrophy	Same or inability to penetrate affected side with oxygen

the appreciable differences in weights of the two glands in the same patient. Absolute proof of the lack of correlation will come from a larger series of bilateral adrenalectomies.

From the present data, it would appear that neither x-ray estimation of increased size nor operative determination of normal or increased weight can be used as a criterion of adrenal cortical function and corticoid activity. A relatively small gland may have high hydrocortisone excretion and a larger one may have low excretion. However, in only 1 case was the hormonally hyperactive gland as small as 5 gm., so that actual discrepancy between the hormonal diagnosis and the pathologic specimen was not large (table 2). If in addition, one takes into account microscopic evidence of hyperactivity, the error is even less.

Fluorocortisone suppression test.[6] A very potent derivative of cortisone can be used for pituitary ACTH suppression. The results are much less reliable, however, for Cushing's syndrome than for the syndromes of androgenic hypersecretion.

9 α-fluorohydrocortisone acetate (Squibb) is given in the ratio of 1 mg. for every 3 mg. of basal 17-hydroxycorticoid excretion in the urine in 4 divided doses

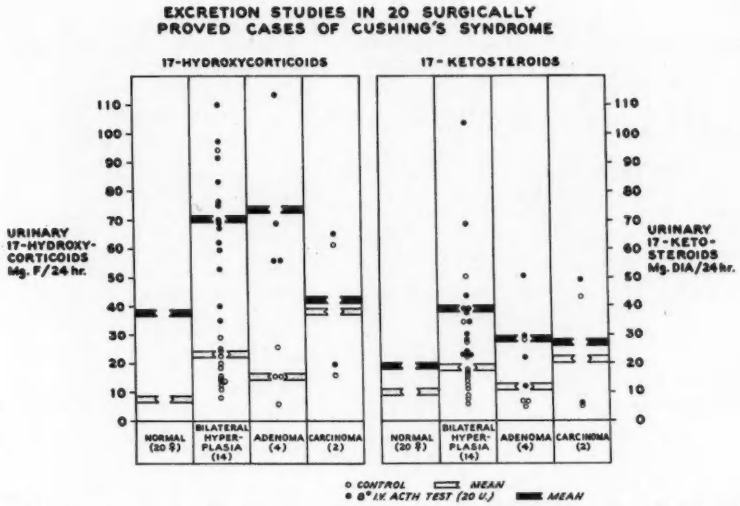

FIG. 2. Baseline and stimulation levels of 17-hydroxycorticoid and 17-ketosteroid excretion in 20 surgically-proved cases of Cushing's syndrome.

TABLE 2. *Reliability of ACTH stimulation test in Cushing's syndrome* (20 cases, surgically verified)

	Total cases	Correctly diagnosed	Equivocal	Error
Hyperplasia or adenoma.....	18	17	1	0
Carcinoma	2	2	0	0

at 6 hour intervals each day for 3 days. A 24-hour specimen of urine is collected on the third day for urinary 17-hydroxycorticoid and 17-ketosteroid determinations.

Hyperplasia causing Cushing's syndrome may yield a 50 per cent or greater fall in corticoid excretion. Adenoma may give no change at all, or a less than 50 per cent fall, and carcinoma, as would be expected, has shown no fall at all. However, the results are so variable that the test is of greater theoretic than practical value in Cushing's syndrome. This is in contrast to the findings in the adrenogenital syndrome.[7]

EXCRETION STUDIES IN THREE ILLUSTRATIVE CASES OF HYPERPLASIA AND CARCINOMA

Hyperplasia. The basal levels, and results of stimulation and suppression in a 24-year-old man with clinical Cushing's syndrome are shown in table 3. Bi-

[6] Goldfein, A., Laidlaw, J. C., Abu Haydar, N., Renold, A. E. and Thorn, G. W.: Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F. New Eng. J. Med., **252:** 415, 1955.

[7] Jailer, J. W., Gold, J. J. and Wallace, E. Z.: Evaluation of "cortisone test" as diagnostic aid in differentiating adrenal hyperplasia from adrenal neoplasia. Am. J. Med., **16:** 340, 1954.

TABLE 3. *24-hour urinary steroid studies*

T.M., male, age 24, UCH 240340	Bilateral adrenal cortical hyperplasia	
	Total 17-OHC	17-KETOS
Control	29 mg. F	50 mg. DIA
ACTH stimulation	97 mg. F	104 mg. DIA
FF suppression	16 mg. F	35 mg. DIA

TABLE 4. *24-hour urinary steroid studies*

D.D., female, age 62, UCH 49257	Adrenal cortical adenoma	
	Total 17-OHC	17-KETOS
Control	15 mg. F	7 mg. DIA
ACTH stimulation	113 mg. F	22 mg. DIA
FF suppression	8 mg. F	4 mg. DIA

TABLE 5. *24-hour urinary steroid studies*

E.P., male, age 12, UCH 242287	Adrenal cortical adenocarcinoma	
	Total 17-OHC	17-KETOS
Control	16 mg. F	5 mg. DIA
ACTH stimulation	19.5 mg. F	6 mg. DIA
FF suppression	17 mg. F	6 mg. DIA

lateral hyperplastic adrenal glands were removed, and the patient has improved since operation.

Adenoma. Excretion studies on this 62-year-old woman with symptoms of Cushing's syndrome are shown in table 4.

Operative removal of the adenoma after roentgen localization allowed the corticoid and 17-ketosteroid excretion to return to normal.

Adenocarcinoma. The findings in a 12-year-old boy with a 2-year history of arrested growth, obesity and hypertension are shown in table 5.

Since the removal of the left adrenal including the 5 cm. encapsulated carcinoma several months ago, he has required full maintenance on cortisone because of the extreme contralateral adrenal atrophy.[8, 9]

ROENTGENOGRAPHIC DIFFERENTIATION

Radiologic techniques. We have advocated a *plain film* coned-down over the adrenal areas[9] but we now find plain roentgenography to be rarely diagnostic in adrenal disorders. Excretory urograms are only occasionally helpful in ruling out confusing renal masses, and retrograde pyelograms have been of no value.

[8] Goldberg, M. B., Gordan, G. S., Deamer, W. C. and Hinman, F., Jr.: Mortality in surgically treated adrenocortical tumors I. Report of 3 cases of Cushing's syndrome due to adrenocortical tumors. Postgrad. Med., **11:** 313, 1952.

[9] Hinman, F., Jr. and Forsham, P. H.: Adrenal surgery and its medical management, in Endocrinology in Clinical Practice, by G. S. Gordan and H. Lisser, Year Book Publishers, Chicago, 1953, pp. 159–163.

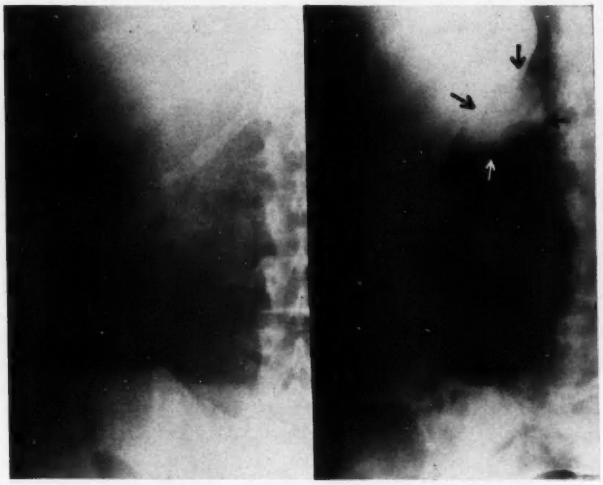

FIG. 3. Poor visualization on excretory urogram, but typical rounded contours on pneumogram of proved adenoma.

TABLE 6. *Reliability of plain roentgenograms and presacral pneumograms in Cushing's syndrome (20 cases, proved surgically)*

	Total cases	Plain films			Presacral pneumograms		
		Diagnostic	No value	Error	Diagnostic	No value	Error
Normal size and hyperplasia	14	0	14	0	13	0	1
Adenoma	4	0	3*	1	4	0	0
Carcinoma	2	0	2	0	1	0	1

* Includes 1 case in which low left kidney suggested left tumor, proved correct.

In 14 cases of hyperplasia, in 3 of 4 cases of adenoma and in 2 cases of carcinoma, the state of the adrenals could not be distinguished on the plain films (fig. 3, table 6). In one case of adenoma, the plain film actually indicated tumor on the opposite side. In contrast, in another case of adrenal adenoma, the left kidney was displaced downward, which was interpreted as evidence of left adrenal tumor. Such a tumor was confirmed by gas studies and removed at operation. However, left renal displacement is not a reliable sign, since Rosenberg in an unpublished study from this hospital found the left kidney lower than the right in the abdominal films of 15 of 100 normal individuals.[10]

Extraperitoneal pneumograms (presacral gas insufflation)[11] have proved most diagnostic especially when combined with tomography (fig. 4, table 6). The value of tomography alone at the time of making the plain film has not been thoroughly

[10] Rosenberg, R. H. Personal communication.

[11] Steinbach, H. L. and Smith, D. R.: Extraperitoneal pneumography in diagnosis of retroperitoneal tumors. A. M. A. Arch. Surg., **70:** 161, 1955.

FIG. 4. Nondiagnostic plain film, helpful pneumogram and diagnostic tomogram of functioning adrenal cortical carcinoma.

FIG. 5. Apparent bilateral hyperplasia in patient with normal hormonal excretion (case excluded from present series).

studied; it may be that the perinephric fat will give adequate contrast in some cases without the confusing dissection produced by gas infiltration.

As has already been pointed out, correlation would not be expected between the x-ray appearance of hyperplasia and the hormonal excretion, since there is no correlation between such excretion and the weight of the gland at operation (fig. 5). However, as is shown in table 6, pneumograms are reasonably reliable if one groups normal-sized and hyperplastic glands together. In other words, tumors were rarely found if the films showed normal or hyperplastic glands.

The single serious error among the cases of hyperplasia was believed to be due to the presence of too much gas. We read the films as showing a large left adrenal tumor and a small right adrenal gland (fig. 6). Operation revealed bilateral hypertrophy (12.9 gm. and 14.8 gm. respectively).

Contralateral adrenal atrophy is a valuable sign of adrenal tumor (fig. 7). However in the 1 case of carcinoma, the right adrenal appeared large by x-ray (the left was not adequately visualized) but was found atrophic on surgical exposure. The tumor of course was then found on the opposite side. Of equal value is the rounded contour of the typical adenoma or carcinoma (fig. 3).

FIG. 6. Error in reading of pneumogram: apparent right adrenal atrophy with tumor on left side, proved to be bilateral hyperplasia.

FIG. 7. Typical pneumogram with tomography showing atrophic right adrenal and tumor on left.

To *summarize* the roentgenographic data, the study of these films has shown certain criteria to be valuable, even though our favorable experience with presacral pneumography is not shared by others.[12]

First, a *rounded or oval mass* on the pneumograms is virtually diagnostic of adrenal neoplasm if corticoid excretion is elevated. A large triangular adrenal associated with contralateral atrophy is also indicative of tumor. Adrenal tumors do not lose their triangular shape until they are large. In one case with normal 17-hydroxycorticoid excretion, a mass considered by some but not all observers to be suprarenal proved to be a pancreatic cyst.

Second, a very *small adrenal* is quite suggestive of neoplasm on the opposite side. Among 6 cases (4 of adenoma and 2 of carcinoma), 4 appeared atrophic which was diagnostically helpful. In the other 2, the small adrenal on the non-

[12] Cope, O. and Raker, J. W.: Cushing's disease. New Eng. J. Med., **253:** 119, 1955; ibid. **253:** 165, 1955.

tumorous side was not properly visualized because of inadequate distribution of gas. However, in one of these last cases the tumor itself could be seen on the other side.

Third, *displacement* of the left kidney below the level of the right kidney is an unreliable sign, since it occurs in 15 per cent of normal individuals.

SUMMARY AND CONCLUSIONS

Hormonal excretion studies and roentgenograms were evaluated for their usefulness in distinguishing adrenal hyperplasia from adenoma and carcinoma in 20 cases of Cushing's syndrome coming to operation.

Baseline determinations of 17-hydroxycorticoids and determinations after stimulation with ACTH in 14 cases of hyperplasia and 4 cases of adenoma showed that a resting level of over 12 mg./day was suggestive of Cushing's syndrome. Post-stimulation levels of over 50 mg./day were diagnostic. In 2 cases of carcinoma, stimulation produced no significant rise of the high basal 17-hydroxycorticoid level. The 17-ketosteroid excretion was similarly recorded but alterations were of less magnitude and importance for the diagnosis of Cushing's syndrome than in syndromes consisting primarily of virilization.

There was no correlation in this group between degree of maximal adrenal hyperactivity as measured by the stimulation tests and the size of the "hyperplastic" gland removed at operation. This has significance for the urologist, since it suggests that he cannot predict adrenal cortical activity from the size of the adrenals either on pneumography or at operation. The diagnosis of Cushing's syndrome therefore rests on clinical observations and steroid excretion studies.

Suppression of 17-hydroxycorticoid excretion with 9-α-flourocortisone acetate was not helpful diagnostically, because of unpredictable variations.

Plain roentgenograms were not helpful in differentiating hyperplasia from tumor, yet presacral pneumograms were diagnostic in all but 2 of 20 cases. Of especial help was the observation of a rounded mass and the finding of contralateral adrenal atrophy.

It is concluded that:

Corticoid excretion after ACTH stimulation tests distinguishes: a) normal adrenals from those producing Cushing's syndrome, b) adrenal hyperplasia and adenoma from carcinoma.

Pneumograms, with tomography, distinguish hyperplasia from tumor.

After using these diagnostic aids in combination, the urologic surgeon can subsequently operate with reasonable confidence of finding the expected adrenal lesion.

VALUE OF CYSTECTOMY IN MANAGEMENT OF CARCINOMA OF BLADDER

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The value of simple cystectomy in the treatment of carcinoma of the bladder is highly controversial. At present, the majority of urologists throughout the country favor other methods of treatment. Although the total number of cases included in our series of total cystectomy for carcinoma is comparatively small, an analysis of our 5-year results leads to some interesting conclusions.

A total 48 cases, all operated upon prior to March 1, 1951, is presented. Simple cystectomy with ureterosigmoidostomy, usually performed in one stage, was performed in all except one patient. In this case, a diverting colostomy was performed at the time of surgery and the ureters transplanted into a rectal pouch. There were two operative deaths (4.2 per cent). Thirty patients died within the 5-year period and 16 survived five or more years, a 5-year survival rate of 33⅓ per cent. This figure compares favorably with that given for other methods of treatment. Furthermore, included in the series were many cases with far advanced carcinoma, undertaken early in our experience, in which surgery was performed with the full realization that the possibility of cure was almost negligible.

Carcinoma was the cause of death in 17 patients. Other causes are listed in table 1. Of significance in this group is the fact that renal failure was the direct cause of death in only three. Of these, one had extensive renal damage with marked bilateral hydronephrosis and hydroureter previous to surgery. Although he had remarkably poor renal reserve, he survived the extensive surgery unusually well, experienced considerable improvement in renal function, and lived a normal active existence for a period of about 18 months. However, he suffered a marked acidosis throughout that entire time requiring large doses of sodium bicarbonate. He was not too co-operative and died presumably of acidosis while visiting in another state. As is noted, the other causes of death cover those diseases that one would anticipate in the age group from which these patients were taken.

Of those who died, the average survival was 18.1 months. Excellent palliation was obtained in almost every instance and we believe that the procedure was fully justified for that reason alone even though it was not curative. Practically all of the cases were graded according to Jewett's classification (table 2). As was anticipated, of those who died 67.6 per cent fell in the class B and C group. However, surprisingly enough 62.5 per cent of the survivor group also fell into this classification, proving that even fairly far advanced carcinoma is occasionally amenable to radical removal. The comparatively small number of cases in the Jewett classification A is due to the fact that only those cases with demonstrable muscle invasion or with a Broders' classification of group 2 or above were treated by cystectomy.

TABLE 1

Renal failure	3
Coronary thrombosis	2
Cerebral thrombosis	1
Hypertensive cardiovascular disease	1
Pneumonia	1
Osteomyelitis of the cervical spine	1
General debility	1
Unknown	3

TABLE 2. *Jewett classification*

	A	B	C	Unclassified
Alive	37.5	37.5	25.0	
Dead	16.72	20.0	47.6	16.6

Values are expressed in per cent.

TABLE 3. *Grade and type of tumor*

	Epidermoid	Transitional Cell			
		I	II	III	IV
Alive	6.3	6.3	37.5	43.6	6.3
Dead	16.7	3.3	30.0	33.3	16.7

Values are expressed in per cent.

Table 3 shows the survival rate according to the grade of tumor. Of note is the fact that 50 per cent of the survivors are in the grade 3 and 4 classification. Also the one case of epidermoid carcinoma is a 5-year survivor. From tables 2 and 3 it is apparent that a very respectable 5-year survival rate has been obtained in spite of the fact that in practically all cases a fairly high degree of malignancy and bladder penetration was present.

The essential facts concerning the 5-year survivors are presented in table 4. None of the patients in this group have clinical evidence of carcinoma at the present time.

A study of the renal status as obtained from excretory urography and blood chemistry findings was obtained on every patient in this group four and a half or more years after surgery. One patient underwent nephrectomy prior to cystectomy and, therefore, there were only 31 renal units available for study. Of these, 22 or 70.9 per cent are considered to be normal having no evidence of or at most a grade 1 hydronephrosis. Of the remaining patients, in only 3 cases is the overall renal status considered as poor.

The point has been frequently made that although patients may survive cystectomy and urinary diversion, many of them are essentially renal cripples and are unable to carry on their usual normal activities. Therefore, we have made a special effort to determine the amount of physical activity which these patients

can perform and find that only two of the group are unable to carry out normal activities and a third is partially disabled. Renal sepsis has been present in five of the surviving sixteen but in every instance it has been readily controlled by suitable antibiotic therapy, and at no time has it interfered to any significant extent with the patient's ability to carry on normal activities.

One of the patients has required reimplantation of ureters into an isolated ileal segment because of progressive hydronephrosis and renal deterioration. This process was progressing although the patient was carrying on normal activities and considerable persuasion was required to convince him of the necessity of additional surgery. An excellent result has been obtained with the ileal seg-

TABLE 4

Name	RT.K	LT.K	Died	Overall Renal Status	Jewett	Grade Tumor	NPN	CO_2	Sepsis	Normal Activities
E.H.	Normal	Normal		Excellent	B	2	25	25	0	Yes
G.F.	No shadow; non-function pre-op.	Normal	7 yrs.	Good	B	1	25 85*	16– 27.7	0	Yes
E.B.	No shadow	No shadow		Poor	A	2	48	14.2	+	No
R.P.	Normal	Normal		Good	A	2	57.5	18	0	Yes
C.H.	No kidney at cystectomy	Normal		Fair	B	2	30.5	14.3	+–	No
F.G.	Normal	Normal		Excellent	A–B	2	20	23.5	+–	Yes
H.C.	Grade 1	Normal		Good	B	3	29	28.6	+	Yes
A.L.	Grade 2	Grade 2 with staghorn calculus		Poor	A	3	34	15	0	Partially
M.L.	Normal	Normal		Fair	A	2	39	16.3	0	Yes
J.S.	Grade 2. Poor function	Normal config. Poor function	5 yrs.	Poor	C	Epidermoid 4	32	19	+	No
A.F.	Grade 1	Grade 1	5 yrs.	Good	C	3	26	26.8	0	Yes
A.K.	Normal	Normal		Good	C	Epidermoid	17.5	20.5	0	Yes
M.T.	Grade 2	Grade 1		Excellent	A	3	31	18	0	Yes
J.K.	Grade 1	Normal		Excellent	C	3			0	Yes
G.K.†	Normal	Normal		Excellent	A	3	20		0	Yes
L.L.‡	Grade 2	Normal		Good	B	3	20	25.9	0	Yes

* Terminal.

† Urinary diversion to isolated rectal pouch.

‡ Ureterosigmoidostomy. Converted to ileal loop after 3½ years because of renal deterioration.

ment, one kidney and ureter have returned to normal pyelographically, the other still maintains about a grade 2 dilatation; and the blood nonprotein nitrogen and CO_2 combining power have been completely normal since the ileal diversion. I believe that this particular case emphasizes the importance of regular periodic observation of all patients with urinary diversion irrespective of type. Furthermore, I believe that to some extent it demonstrates the superiority of the isolated ileal segment as a means of urinary diversion.

An autopsy was obtained on all three of those patients who survived more than 5 years and died subsequently. Several lessons have been obtained from these postmortem examinations and a brief evaluation of each is in order.

G.F. survived for 7 years. During his sixth year marked hypertension with a pronounced azotemia developed. Up until that time he was performing regular activities as a day laborer and actually continued to do so until within about one month of his death. He had had a nonfunctioning atrophic kidney on the right prior to the original surgery and it never became functional; however, the left pyeloureterogram was normal in every respect on repeated examinations as long as 6 years postoperatively. When the nonprotein nitrogen rose, it was believed that the elevation was secondary to malignant hypertension. However, at autopsy the patient was found to have numerous calculi with a definite hydronephrosis in the kidney which pyelographically had remained normal for a 6-year period. Since there was no evidence of pelvic dilatation or calculi approximately 9 months before death, I believe it is possible that the production of calculi occurred as a terminal event but they undoubtedly contributed to the fatal outcome. This patient originally had extensive recurrent grade 1 papillomatosis of the bladder. There was no evidence of carcinoma at autopsy.

J.S. survived for 5 years and died of multiple cortical abscesses of both kidneys. During the entire period of his survival he had shown a grade 2 hydronephrosis on the right and a normal configuration on the left, with bilateral poor function to excretory urography. His renal status was always listed as poor. This patient resisted all persuasions that he submit to diversion of the colon above the ureterosigmoidostomy or any other type of urinary diversion. The character of his lesion was recognized and had he been more co-operative, a more favorable result might have been obtained. Although he had an epidermoid carcinoma, grade 4 with penetration through the entire bladder wall, careful search for carcinoma at autopsy revealed no signs of residual tumor. This case again reemphasizes the fact that every patient with bladder carcinoma should be given a chance at cure by radical means, even though the lesion appears to be far advanced. If there are no demonstrable lymph node metastases and the bladder is not fixed laterally, cystectomy should be done.

A.F. had chronic lymphatic leukemia which was under fair control. In addition, he had a grade 3 carcinoma with penetration through the entire bladder wall for which cystectomy and ureterosigmoidostomy were performed. Convalescence was uneventful and although the ureters showed a mild, grade 1 dilatation bilaterally and his overall renal status was listed only as good, he enjoyed excellent health as far as the kidneys were concerned. Thrombophlebitis eventu-

ally developed and the patient died of pulmonary embolus. At autopsy the upper urinary tract was found to be in good condition. There was minimal ureteral dilatation and the ureterosigmoidostomies were open and functioning well. There was no evidence of carcinoma anywhere in the pelvis. However, a single solitary nodule about the size of a hickory nut was found in the liver which, on microscopic section, was found to be transitional cell carcinoma. This disconcerting feature emphasizes a fact with which we are all familiar, namely, that although there may be no clinical evidence of carcinoma, some of our survivors may be harboring occult metastatic carcinoma at the present time and a 5-year survival certainly does not mean that there is a cancer cure.

SUMMARY

A closed series of 48 cases on whom cystectomy and ureterosigmoidostomy have been done for carcinoma of the urinary bladder is presented. There are 16 five-year survivors, a 33⅓ per cent survival rate.

Overall renal status in this group has been acceptable.

Of the group of survivors, all but three have been able to carry on normal duties. In my opinion cystectomy for carcinoma of the urinary bladder still has a significant place in the management of that highly lethal disease.

DISCUSSION

Dr. J. A. Campbell Colston (Baltimore, Md.): I'd like to ask Dr. Hinman a question. I know he emphasized the fact that his paper contained nothing about treatment, but I would just like to ask him briefly about the surgical approach he uses in cases where he is quite sure on which side the tumor is, and also when he is in doubt.

Dr. Roger C. Graves (Boston, Mass.): May I ask Dr. Cordonnier if he has done pelvic lymph node sections with his cystectomies.

Dr. John K. Lattimer (New York, N. Y.): Did any of the 5-year survivors have lymph nodes outside the bladder at the time of operation?

Dr. Hugh Judge Jewett (Baltimore, Md.): I would like to ask Dr. Cordonnier one question.

This is a very creditable series of cases, with beautiful results. I should like to know whether Dr. Cordonnier has determined the percentage of patients with perivesical fat involvement who lived 5 years, the percentage of patients in the series with deep muscle involvement who lived 5 years, and the percentage of patients with superficial muscle involvement who lived 5 years.

Dr. C. D. Creevy (Minneapolis, Minn.): I'd like to ask Dr. Cordonnier, is deliberate palliative diversion in inoperable carcinoma worth while?

Dr. Frank Hinman, Jr. (San Francisco, Calif.): In answer to Dr. Colston's question, we think we have, as most of us have, tried every known and some unknown approaches in these patients. My own feeling at the present time, and the plan that I carry out, is, if we have a known tumor which is rather large, like some of those you saw on the pneumograms, which lies rather high, and we would like to do as radical an approach as we can, we would approach through a high incision. I prefer the transthoracic incision between the ninth and tenth ribs, dividing the angle of the tenth rib if that is necessary, approaching transpleurally and transdiaphragmatically.

However, in the hyperplasias and in the smaller tumors that look easy, I think by all odds the eleventh rib approach is the operation of choice. We have a little difficulty teaching the residents this operation, because, as soon as they go through the bed of the rib, they want to push the pleura and diaphragm up, and then, of course, they enter the pleural cavity. We have found that if we make them deliberately dissect the diaphragm off the undersurface of the twelfth rib by sharp dissection, that the whole base of the pleura will rise. They may never see the pleural reflection, or, if they do, it is found riding up on the diaphragm. Thus they stay out of trouble.

As far as what we do if we're in doubt as to the diagnosis, we go through the eleventh rib on one side and repeat the procedure on the other side, if indicated.

At the present time, as of this week, we are doing bilateral total adrenalectomies, but next week we'll probably be doing subtotal adrenalectomies again, leaving in perhaps one-fifth of an adrenal. We would operate on a single side, doing both sides at the same sitting, or doing them at separate times.

One other thing. I have brought along with me some multilith outlines of the

steps in diagnosis and differentiation that we have talked about this morning, giving the figures for those of you who might be interested. Some of you may find them useful for residency training.

Dr. John L. Emmett (Rochester, Minn.): May I compliment Dr. Campbell on a most excellent presentation.* Any contribution to the urologic problem in children with myelodysplasia is most welcome.

May I call your attention to the fact that up to now about all the progress we have made with this discouraging condition is by entirely bypassing the neurologic lesion and substituting other mechanisms to carry on micturition. Thus by resecting the vesical neck and substituting abdominal pressure or manual (credé) expression of the bladder, some children can be kept reasonably dry and free from infection.

Dr. Campbell has shown some limited improvement in vesical function with accompanying reduction in residual urine as a result of his intraspinal surgery. I would like to suggest that after the optimum degree of improvement has been achieved by this procedure, further improvement might be obtained with transurethral resection of the vesical neck. It seems quite possible that these procedures may complement each other.

Dr. James B. Campbell (New York, N. Y.): I would much rather have my partner in crime, Dr. Lattimer, discuss the vesical neck, because I'm not qualified in that field. Right now in the laboratory, we are trying to study the innervation of this structure, and I will say this for a cat—man I cannot discuss at this point—bilateral pudendal section does not change the status of continence. Even a cat with a single dorsal-sacral nerve root or a single ventral-sacral nerve root, or any of the combinations I threw on the wall, will retain continence with resection of the pudendal nerve.

I hope we will have a report for the literature in a year on innervation in the cat, and I hope later we'll be able to do that in man.

Dr. Bors has done an enormous amount of work on this, and we have a constant exchange of information, so if you don't mind, I won't say anything about the vesical neck.

Dr. J. J. Cordonnier (St. Louis, Mo.): In answer to our first question about lymph node dissection, I am afraid I am going to sound a little unsurgical. We did lymph node dissections for a period and found that those with positive nodes died within a year. It would seem that radical lymph node dissection contributed little to longevity. Convalescence was longer and more complicated. If positive lymph node involvement has been found at operation, we have not performed a cystectomy, but have done urinary diversion when indicated.

Now, as regards Dr. Jewett's question, we have 37.5 per cent who have had superficial invasion only; that is, no penetration of the muscularis. The 37.5 per cent had superficial penetration part of the way through the bladder wall—what we would call a Jewett classification B; and 25 per cent had penetration through the entire bladder wall.

Now, whether there was that involvement or not depends on the pathologists.

* Dr. Campbell's presentation will not be published at this time.

I didn't go over all these specimens personally, but they did list them as having invasion through the entire bladder wall in approximately 25 per cent of the patients.

DR. JEWETT: How many of them lived?

DR. CORDONNIER: That's the percentage of the total survivors.

Sixteen per cent were A's, 30 per cent were B's, 40 per cent were C's, and 16.6 per cent were unclassified.

As far as deliberate palliation is concerned, I think that that enters into a philosophical point, because some people feel that perhaps it's better for these people to die of uremia, and I think if they have advanced cancer it probably is. If the carcinoma seems to be localized in the bladder, but is fixed beyond any possibility of radical removal, we have been diverting into an ileal segment, followed by betatron therapy. It is much too early to tell whether we are going to get palliation from that type of treatment.

SYMPOSIUM ON REMEDIAL RENAL HYPERTENSION

PRESIDENT HECKEL: Dr. Taylor has arranged a very interesting and, I would say, a very important symposium on "Remedial Renal Hypertension." We are very privileged to have Dr. Kendall Emerson, of Boston, as a participant in this symposium and he is going to open the symposium by talking to us on "The Endocrine Kidney."

DR. KENDALL EMERSON: It is a real privilege to be asked here to try to start off the non-urological portion of this symposium on the question of the subject of renal hypertension.

[Formal papers were not prepared by Drs. Emerson and Harrison. Dr. Emerson discussed the endocrine factors related to hypertension and pointed out the interrelations of pituitary and renal factors in the production of hypertension. The mechanism of production of renin and hypertensinogen by renal lesions was elucidated.]

PRESIDENT HECKEL: This symposium will be continued by Dr. Hartwell Harrison who will talk to us on "The Urologic Aspects of Management of Renal Hypertension."

[The following outline was utilized in the discussion by Dr. Harrison of renal hypertension and each condition was illustrated roentgenographically and appropriate pathologic material was also presented.]

I. Primary vascular lesions producing hypertension
   1. Embolus with infarction of the kidney
   2. Renal vascular thrombosis
      a. Spontaneous
      b. Traumatic
      c. Aneurysm of the renal artery
      d. Renal arterial stenosis with post-stenotic dilatation
      e. Nephrosclerosis

II. The nephritides
   1. Pyelonephritis
   2. Glomerulonephritis

III. Congenital anomalies
   1. Polycystic disease
   2. Hydronephrosis
   3. Megaloureter
   4. Stenosis of vesical neck
   5. Hypoplasia of the kidney with pyelonephritis

IV. Acquired obstructive uropathy
   1. Prostatic hyperplasia
   2. Nephrolithiasis
   3. Urethral stricture
   4. Extrinsic ureteral obstruction (e.g. carcinoma of cervix, endometriosis, lymphoma, carcinoma of rectum)

With the permission of the President, Dr. Norris Heckel, Dr. Harrison then called on Dr. George Prather to present a case of renal arterial embolization producing a non-functioning kidney with subsequent recovery of the kidney to normal function without surgical intervention.

Preceding Dr. Prather, Dr. William Engel was called on to present the work of himself and Dr. Eugene Poutasse on bilateral stenosis of the renal artery in producing hypertension, and the surgical correction thereof.

DR. HARRISON: I would like at this point to call on Dr. Engel to further discuss the theory and his experience and that of Dr. Poutasse with renal hypertension.

DR. W. J. ENGEL (Cleveland, Ohio): Knowing of our interest in this subject, Dr. Harrison was kind enough to suggest that we bring a few cases along to amplify his remarks. My remarks will be restricted to obstructive renal arterial disease as a cause of hypertension.

Most of the cases that I am showing have been worked up with our associate, Dr. Poutasse, whose enthusiasm has lent a great deal to our knowledge of this subject. I think it is quite appropriate that a medical man should open this symposium because we feel that a medical man should first see these cases and filter them out from the large group of patients who have hypertension.

In making the diagnosis of an obstructive disease of the renal artery, the procedure of greatest value is renal angiography. This we accomplish by means of translumbar aortography. We presented an exhibit at the recent American Urological Association meeting and I was impressed by the number of men visiting the exhibit who hesitated to do aortograms because of the fear of complications. We feel that the dangers of this procedure have been overemphasized and a recent lawsuit has further exaggerated the fear of aortography. With certain technical precautions we believe aortography is a relatively safe procedure.

We like to use small amounts of the contrast medium. After doing the aortic puncture we inject 10 cc of a 25 per cent solution of hypaque and make a film to determine if the needle is properly placed. I believe some of the complications have been due to extravasation of the contrast material or to accidental puncture and injection of one of the smaller branches of the aorta.

Having determined that the needle is properly placed, we then make the final aortogram by injecting 10 to 12 cc of 50 per cent hypaque, using a compression pad under the lower abdomen for the purpose of slowing aortic blood flow. Using this technique we have now done more than 500 aortograms without significant complications. Most aortograms can be done under local anesthesia without difficulty.

(Slide) One of the early cases that I had the privilege of seeing was a young man 26 years of age who came in with a very severe malignant hypertension, grade 4, eye ground changes, and everything that goes with the condition. The history was that 5 weeks previously he had had an obscure illness and one bout of right flank pain which was thought to be due to pyelitis which improved with treatment. Then hypertension was observed which quickly progressed to the malignant phase.

As you look at this excretory urogram, you could easily interpret it as normal

which we did originally—but with the history of very sudden onset of hypertension it seemed to me we had to do an aortogram.

Before moving from this urogram I want to show in retrospect one of the things that we have observed. The renal mass on the right side is somewhat less than it is on the left side (indicating), and that may be a hint to you.

On the aortogram one can see these two main branches of the renal artery completely occluded, (indicating) and this one branch seems to carry the nutrition to the kidney.

(Slide) Here is the gross specimen following nephrectomy, showing the very large thrombosis of the renal artery.

Immediately following nephrectomy this patient had a severe hypotensive reaction that required active supportive treatment for 24 hours. It resembled very much the postoperative reaction we used to see following removal of pheochromocytoma. The patient made a complete recovery, the blood pressure was restored to normal levels and has now remained so for a year. Furthermore the eye ground changes all returned to normal.

(Slide) This patient was 50 years of age. He had had an appendectomy for a suppurative appendicitis in May. He had a very stormy convalescence, but following his recovery a severe malignant hypertension developed. The excretory urogram shows good function on the right side (indicating), and those of you who are close can see only a trace of "dye" here which was excreted in the lower calyx of the left kidney.

This is a retrograde pyelogram, to show you that you cannot pick out these cases by retrograde pyelography since in this case the pyelogram is normal.

(Slide) The aortogram shows a normal circulation on the right side. (Indicating) On the left there is no main renal artery, but you can see a small accessory artery coming to the lower pole of the kidney.

(Slide) This is a color photograph of the kidney. Here is the thrombotic main renal artery. This is the accessory artery (indicating) going to the lower pole. You can see the normal markings between cortex and medulla only at the lower pole. The rest of the kidney takes on a diffuse liver color.

Following the removal of that kidney, this patient had a return of his blood pressure to essentially normal levels. The eye ground changes returned to normal. Now more than a year after nephrectomy this patient remains well, though it should be reported that his blood pressure has risen to levels of mild essential hypertension.

(Slide) Here is a young man 30 years of age who had a bout of right kidney colic, thought to be due to a stone. At that time, the x-rays showed no stone shadow. An excretory urogram showed no function in that kidney. He finally cleared up from his acute bout of pain, and a later urogram showed return of function on that side, which supported the thought that he had probably had a non-opaque stone. However, following that, severe malignant hypertension developed.

(Slide) Here's an aortogram made on this patient. Observe that there is a lower branch of the renal artery that is missing (indicating), so we have circulation only through this upper part of the kidney.

Dr. John Ryan took out this kidney and his blood pressure returned very promptly to normal.

(Slide) This chart is simply to show the drop in pressure. The pathologist at the hospital was good enough to send us sections, and a very interesting thing developed.

(Slide) This is the artery, which shows the marked narrowing of the lumen.

(Slide) This is the interesting one. The pathologist had the good fortune to section this kidney between the line of ischemia and the normal portion, and you can see, I think, that this is not unlike the endocrine kidney that you spoke of, Dr. Emerson, and this is the normal line. (Indicating)

(Slide) This patient is a boy 16 years of age who came in with malignant hypertension. The excretory urogram shows good function. The retrograde pyelogram was essentially normal. The aortogram shows bilateral narrowing of the renal arteries, and on the left side there is a jet aneurysmal dilatation of the artery.

Well, this was quite a problem, and Dr. Poutasse enlisted the help of Dr. Humphries, who is our vascular surgeon, and they felt the only chance was bilateral renal artery graft.

(Slide) This is the wax model of about what the situation looked like, this being the narrow point on the left side (indicating), and this being the narrow point on the right side.

(Slide) Here is a photomicrograph of a cross-section of one of these renal arteries showing the very marked fibrous intimal proliferation of that vessel. We have had three of these bilateral renal arterial occlusions of that type. The other two died, but they all showed the same changes. Our pathologist is inclined to think that this may represent some separate pathological entity.

(Slide) This is a plastic model reconstruction of the bilateral arterial graft. I think you might be interested in a word about the technical considerations. The left side was done first and about 12 days later, when it had been ascertained that good function had returned, the right side was grafted. The graft was first attached to the aorta without disturbing the normal circulation. The renal artery was then clamped, divided, and anastomosed to the distal end of the graft. The period of renal ischemia was about 12 minutes on the left side and 14 minutes on the right.

This is a postoperative aortogram on this patient. (Slide) I think Dr. Poutasse showed courage in doing this. I'm not sure that I would have, but you can see the beautiful blood supply that exists in both kidneys, and the next slide shows the postoperative intravenous urogram with excellent bilateral function.

In reporting this case to you I claim no credit because all I did was stand on the sidelines and cheer. As far as I know, this is the first successful bilateral renal arterial graft.

Dr. Harrison: I want to call on Dr. George Prather at this moment.

Dr. George C. Prather (Brookline, Mass.): I don't have anything like Bill Engel had to show. Hartwell was interested in this next patient.

(Slide) This was a man aged 50 who, one morning in Wellesley, had acute left flank distress with nausea and vomiting, and was admitted to one of those "outside hospitals." I assume at that time it was impossible to make a diagnosis by feeling his abdomen.

We considered his excretory urogram, which you see, and there was no evidence of excretion by the left kidney. This was done on August 22, 1955.

(Slide) On the next day came the retrograde pyelogram, which looked normal. The only thing that I knew to put those two things together—that is, a normal retrograde and no excretion on the intravenous urogram—was an infarct, so, on August 27, three days after this, my associate did an aortogram, which shows circulation to the right kidney (slide), but, in our opinion, little or no circulation to the left.

That seemed to confirm the diagnosis of infarct, so, with the help of a medical man, we decided that he had valvular heart disease.

I, not wishing to do a valvulotomy, transferred him to the Brigham, where he proceeded to have heart surgery.

Three months later (slide), Hartwell and Hathorn Brown did an excretory urogram, which I think demonstrates a return of function to the left kidney, but if one observes the size of the original retrograde and the size of this later intravenous pyelogram, there has been a diminution in the size of the left kidney. This has been our experience in other instances of proven infarct to the kidney, and as far as I know, about three to four months after the accident occurs, there is always evidence of diminution in the size of the kidney.

This subject is of considerable interest, and those of you who heard Homer Smith last week* and listened to his remarks, may have gotten the same impression—or a different impression, perhaps—than I did. It seems to me that he was acting as official executioner to those who believe that unilateral renal disease is the cause of hypertension. That statement may be a little too severe, because if I understood him correctly, he was very much against removing a kidney for hypertension if, in the opinion of the urologist, the kidney should not be removed because of urological evidence.

His criteria, of course, are pretty severe, and as I see it, he's got the guillotine right down pressing on the neck of those who still advocate removal of a kidney for hypertension, but without demonstrable pyelographic deformity, but he hasn't actually stepped on that knife. There's still a chance for others to speak up.

* J. Urol., **76**: 684, 1956.

RESULTS OF NEPHRECTOMY IN HYPERTENSIVE PATIENTS

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Since Butler's[1] original article (1937) describing excellent reduction of hypertension by excision of an atrophied kidney, many papers on this subject have appeared. One of the early studies was that of Barker and Walters,[2] who detailed the results in 5 cases observed at the Mayo Clinic. More recently, Barker[3] outlined the results of surgical treatment for unilateral renal disease in 100 patients who had hypertension and stated that the results 2 or more years after nephrectomy were good in 45 per cent, fair in 19 per cent and poor in 27 per cent; 9 per cent of the patients had died. Braasch[4, 5] also has written on this subject.

Smith,[6] in 1948, reviewed the literature up to that time and presented an analysis of 242 cases reported by various authors. He concluded that good results had been obtained in only 19 per cent of all cases in which unilateral nephrectomy had been performed in the hope of permanently reducing hypertension. He expressed the view that conclusions regarding good effects could not be drawn until the patient had been followed for at least 1 year, during which time the blood pressure should remain at or below a level of 140 mm. of mercury systolic and 90 diastolic.

While one might speculate how one can select the particular patients who will be improved by nephrectomy so that useless operation can be avoided in others, no data exist that will provide reliable answers. Schroeder and Fish,[7] in 1940, suggested the criteria of recent onset of hypertension, unilateral renal involvement with diminished renal function, normal function in the other kidney, absence of retinitis and the presence of a persistently increased blood pressure. To these criteria Perlmutter and Hermann[8] suggested adding that the kidney to be removed should be greatly reduced in size. Some years ago, as a co-author with Pearman and Allen, I[9] made the statement that, "Statistical studies deal-

[1] Butler, A. M.: Chronic pyelonephritis and arterial hypertension. J. Clin. Invest., **16:** 889–897, 1937.

[2] Barker, N. W. and Walters, Waltman: Hypertension and chronic atrophic pyelonephritis—Results of nephrectomy. J. A. M. A., **115:** 912–916, 1940.

[3] Barker, N. W.: Hypertension and unilateral renal disease. M. Clin. North Amer., **35:** 1041–1050, 1951.

[4] Braasch, W. F.: The surgical kidney as an etiologic factor in hypertension. Canad. M. A. J., **44:** 9–15, 1942.

[5] Braasch, W. F.: End results following nephrectomy in patients with hypertension. J. Urol., **68:** 6–10, 1952.

[6] Smith, H. W.: Hypertension and urologic disease. Am. J. Med., **4:** 724–743, 1948.

[7] Schroeder, H. A. and Fish, G. W.: Studies on "essential" hypertension. III. The effect of nephrectomy upon hypertension associated with organic renal disease. Am. J. M. Sc., **199:** 601–616, 1940.

[8] Perlmutter, Martin and Hermann, H. B.: Apparent two-year cure of nephrogenic hypertension. A. M. A. Arch. Int. Med., **91:** 808–811, 1953.

[9] Pearman, R. O., Thompson, G. J. and Allen, E. V.: Urographic evidence of renal lesions in a series of patients suffering from essential hypertension. Proc. Staff Meet., Mayo Clin., **15:** 467–471, 1940.

ing with the question of relationship of renal disease to hypertension are likely to be misleading. In our estimation, the question can be answered accurately in one way only: by determining the effect on hypertension of removal of surgical lesions of kidneys."

PRESENT STUDY

The present article gives data concerning a consecutive series of cases observed at the Mayo Clinic from 1940 through 1954. It includes some of Barker's cases but not the earliest ones. In addition to the effects following removal of atrophic kidneys, the effects of nephrectomy done for hypertensive patients with a variety of other renal diseases will be summarized.

Almost 3,000 patients were subjected to unilateral nephrectomy at the clinic during the 15-year period just mentioned. A diagnosis of hypertension was made preoperatively in 344 (about 11 per cent). The records of these patients were studied. For several reasons, 7 patients were not included in the study.

Of the 337 remaining patients (194 females and 143 males) who were subjected to nephrectomy, 39 had renal tumors, each of 119 had a kidney that either was atrophied or hypoplastic and the remaining 179 had various renal conditions, such as hydronephrosis, tuberculosis, calcareous pyelonephritis, including staghorn calculus, renal cysts (but not congenital polycystic disease), pyonephrosis, subcapsular calcified hematoma and aneurysm of the renal artery.

The diagnosis of hypertension in these cases was made by an internist after complete study. Hypertension was recorded as mild in some cases but in the large majority it was moderate and sometimes severe in character. No case in which the diagnosis was questionable has been included.

In determining the results after nephrectomy, the opinion as to the effect on the patient's blood pressure in the majority of cases was that expressed in the records by both internists and surgeons at the time they had charge of the patient.

A large majority of the patients who were thought to have obtained a good effect were re-examined some years later at the clinic and the determinations of blood pressure often were made by the same physician who examined them preoperatively.

In determining the results of surgical treatment, a good early effect does not mean that the blood pressure merely decreased 40 or 50 mm. of mercury from extremely high levels and remained above 140 mm. systolic; it means, on the contrary, that the pressure leveled off at values less than 140/90 and stayed there until the patient had recovered from the operation, had left the hospital and was dismissed from the clinic. Good late effects were listed according to Smith's definition; the blood pressure in these patients remained at a level below 140/90 for more than a year and in some instances up to 14 years after operation.

RESULTS

Of the 39 patients with tumors, 34 had hypernephromas, four had epitheliomas of the renal pelvis and one had an encapsulated neurofibroma. A good early

effect on the hypertension was observed in 12 of these patients (31 per cent). After a year, however, only 5 patients (13 per cent) had normal blood pressure; four of these 5 patients had hypernephromas and one had an epithelioma of the renal pelvis.

In this series of 337 patients, 29 underwent sympathectomy in addition to nephrectomy. In the opinion of the physician, the urologist and the neurologic surgeon, this combined operation provided the best chance for relief of the hypertension. Nineteen of these patients had atrophic pyelonephritis and 10 had other types of unilateral renal disease.

The difficulty of evaluating the results of nephrectomy in patients subjected to these combined operations is apparent. In fact, such evaluation probably is impossible. However, if only a unilateral sympathectomy and nephrectomy are performed and the blood pressure decreases to a normal level, Uihlein[10] has stated that this good effect probably is obtained from excision of the kidney. Unilateral sympathectomy was combined with nephrectomy in 10 of these 29 patients. Three of these patients had excellent results; two of the three had atrophic pyelonephritis and one had nonatrophic pyelonephritis with calculi. Additional patients who were benefited were included in the 19 for whom bilateral two-stage sympathectomy as well as unilateral nephrectomy was done. These cases will not be analyzed further because of the difficulty in their evaluation.

Excluding from further study the 39 patients with renal tumors and the 29 who had a combination of sympathectomy and nephrectomy, there remain 100 patients with atrophic pyelonephritis and 169 who had miscellaneous surgical renal disease.

It might be well to dwell on how the diagnosis of atrophic pyelonephritis is made and how one distinguishes between a kidney that has atrophied because of infection or other causes and the so-called hypoplastic kidney. Emmett and associates[11] stated after an exhaustive review that it was impractical and almost impossible to attempt to distinguish these conditions clinically, pathologically or urographically with any degree of accuracy. I have, therefore, grouped all the shrunken kidneys in one category.

Barker and Walters[2] noted hypertension in 26 (46 per cent) of 57 cases in which a diagnosis of chronic atrophic pyelonephritis was made urographically. Baggenstoss and Barker,[12] after an intensive necropsy study of 84 cases of unilateral renal atrophy and 13 cases thought to represent hypoplasia, reviewed the clinical records of the patients concerned and found that 40 per cent had hypertension before their death. Both these studies appear to indicate more than a casual association between the two conditions. Evidence in support of this theory should result from a comparison of both early and late results of nephrectomy in patients with atrophic kidneys and the results in the group that includes all other unilateral renal disease (tables 1 and 2). These data indicate that better results

[10] Uihlein, Alfred: Personal communication to the author.

[11] Emmett, J. L., Alvarez-Ierena, J. J. and McDonald, J. R.: Atrophic pyelonephritis versus congenital renal hypoplasia. J. A. M. A., **148:** 1470–1477, 1952.

[12] Baggenstoss, A. H. and Barker, N. W.: Unilateral renal atrophy associated with hypertension. Arch. Path., **32:** 966–982, 1941.

TABLE 1. *Early* results after nephrectomy for hypertension associated with severe unilateral renal disease*

Disease	Total patients	Good effect		Poor effect	
		Patients	Per cent	Patients	Per cent
Atrophic pyelonephritis	100	63	63.0	37	37.0
All other renal conditions	169	64	37.8	105	62.2

* One month after operation or at time of surgical dismissal.

TABLE 2. *Late* results after nephrectomy for hypertension associated with severe unilateral renal disease*

Disease	Total patients traced	Good effect		Poor effect	
		Patients	Per cent	Patients	Per cent
Atrophic pyelonephritis	64	35	54.6	29	45.4
All other renal conditions	100	25	25.0	75	75.0

* One year or more after operation.

TABLE 3. *Effect of nephrectomy for hypertension in renal diseases other than atrophic kidney (excluding tumor)*

Disease	Patients	Good early effect	Good effect, 1 to 15 years	Poor or no effect
Hydronephrosis with or without stones	80	33	15	47
Chronic pyelonephritis with or without stones, including staghorn type	58	24	8	34
Simple cyst, single or multiple	10	1	0	9
Tuberculosis	16	4	1	12
Miscellaneous	5	2	1	3
Total	169	64*	25	105†

* Twenty-two were followed less than 1 year.

† Forty-seven were followed less than 1 year.

are obtained after nephrectomy for atrophic pyelonephritis than can be expected fater nephrectomy for other types of unilateral renal disease. No provision has been made in these tables for fair results; if any doubt occurred, results were classed as poor.

This arbitrary division into good or poor effects refers almost entirely to the blood pressure. A substantial number of patients whose blood pressure did not decrease to normal levels benefited greatly from the operation. Headaches disappeared and general health improved; many stated unequivocally that the nephrectomy undoubtedly was responsible for such improvement. They did not take medicine of any kind. The blood pressure in some patients remained at a normal level for years but after 10 or 12 years it gradually increased (for example, to 170/110), whereas prior to nephrectomy it may have averaged 230/140. It

would be difficult to deny that such a patient had profited from operation, but such patients are listed as having poor effects.

Of the patients who had atrophic pyelonephritis, 70 per cent were female; this condition, as observed clinically, apparently predominates in the female sex. Benefit obtained from nephrectomy appears to occur about equally in each sex.

Whereas 80 per cent of the patients who had atrophic pyelonephritis were 50 years of age or less, only 48 per cent of those with other conditions were 50 or less. Further review was made to see whether the results of operation were better in the younger patients in both groups than they were in older patients; significant differences could not be found.

Results in the various types of renal disease other than atrophic kidney are summarized in table 3.

COMMENT

The early effects of removal of a diseased kidney often are extremely striking. Routine preoperative and postoperative measurements of blood pressure, both systolic and diastolic, show a rather dramatic reduction in pressure when it is going to occur. This generally takes place within the first 2 or 3 days. Sometimes the pressure goes below the value where it finally levels off. In those patients who were not benefited by operation, the postoperative blood pressure usually leveled off at a value near the preoperative reading within 24 hours. I was unable to find a single case in which benefit was delayed for several months but finally occurred. It appears that the reduction in blood pressure will be apparent very early in the postoperative course if a good permanent effect is to be secured from nephrectomy.

All the kidneys were subjected to careful pathologic study in the hope of finding some histologic difference that would contrast definitely with the findings in kidneys removed from patients who did not have hypertension. Nothing specific could be found. In many cases, vascular sclerosis or pronounced thickening of the vessel wall was observed but its extent and severity were by no means indicative of the results that followed operation. The presence or absence of infection apparently did not play a determining role; removal of an uninfected hypoplastic kidney with thin arteries sometimes produced excellent results, while excision of an infected atrophic kidney supplied by extremely sclerotic vessels had no effect whatever. Likewise, some patients were benefited permanently by removal of an infected kidney containing either multiple calculi or a large staghorn calculus, whereas the majority of those having practically identical lesions experienced no reduction of blood pressure.

Renal damage was extensive in all the cases included in this series, with the exception of those in which hypoplasia was present. Nephrectomy was indicated in the majority of instances because of the extent of disease, whether or not hypertension was associated. However, in the case of small or atrophic kidneys, there were usually no localizing symptoms to call attention to the abnormality.

As already indicated, this series represents only about 11 per cent of the total number of patients on whom nephrectomy was performed in the period under

consideration. The remainder who had nephrectomy did not have hypertension. In addition, many patients with surgical renal disease were subjected to conservative procedures, such as pelviolithotomy, plastic operations on the renal pelvis, partial nephrectomy or nephrostomy; some of these patients had associated hypertension. The effect of these surgical procedures on the blood pressure has not been investigated recently.

One should not be disappointed or discouraged by the afore-mentioned lack of a method for accurate selection of those patients who would be certain to obtain permanent reduction of blood pressures after nephrectomy. The fact remains that reduction or elimination of hypertension has followed nephrectomy in a substantial percentage of patients in whom severe unilateral renal disease is present. Unless specific contraindications to operation can be found, it would appear unwise to postpone nephrectomy for fear of not relieving the patient of the distressing symptoms caused by his severe hypertension. Removal of a diseased kidney can be accomplished with extremely little risk to the patient. Furthermore, as a rule, the disease is so far advanced that no point exists in saving the kidney. The patient has much to gain and little to lose.

SUMMARY AND CONCLUSIONS

A study has been made of 337 cases in which a combined diagnosis of hypertension and severe unilateral renal disease was made and in which nephrectomy was performed at the Mayo Clinic during a 15-year period.

Comparison of the results of nephrectomy for an atrophied kidney contrasted with those following nephrectomy for other severe unilateral renal disease reveals that a much better response insofar as reduction in blood pressure is concerned is observed in the atrophic group.

Nephrectomy should be done for the hypertensive patient who has severe disease in one kidney and whose other kidney is normal, providing, of course, that other conditions which prohibit operation are absent.

Nephrectomy provides permanent reduction of the blood pressure to normal levels in at least 50 per cent of cases in which an atrophic kidney was present and in about 25 per cent of cases of all other surgical renal disease, with the exception of tumor.

DISCUSSION

Dr. William P. Herbst (Washington, D. C.): I wonder if Dr. Emerson would give us an appraisal of the value of the differential renal salt excretion tests, and also how does he compare the practical clinical responses following nephrectomy, and bilateral adrenalectomy.

Dr. David M. Davis (Philadelphia, Pa.): I'd like to ask Dr. Harrison or Dr. Emerson, or either of them, what is their opinion, or what is their guess, as to why one of the identical twins developed glomerulonephritis and the other did not.

Dr. W. E. Kittredge (New Orleans, La.): I would like to add one more case to the series which Dr. Engel has shown you.

We recently saw a child of ten with hypertension of recent onset who proved to have a congenital solitary left kidney which, however, had normal function, was normal by intravenous pyelography, and was not infected. Despite this, an aortogram showed a congenital stricture of the renal artery, similar to those just shown you. One of our vascular surgeons operated upon her with the original intention of resecting the stricture and carrying out an arterial graft. When it proved technically difficult, however, to dissect out the area of stricture, he elected to remove the spleen and graft the splenic artery into the renal artery, distal to the stricture.

There was some concern at first, as to whether the blood pressure in the splenic artery would be adequate to accomplish the desired effect, but I can say that it worked quite well. The child's pressure returned to normal, and has remained normal thoughout the eight-month period since the operation. As Bill has said, cases such as these emphasize the fact that, even though a kidney may show normal function and a normal pyelogram, occasionally an aortogram may demonstrate obstructive pathological processes in the renal artery capable of causing renal hypertension.

Dr. George F. Hoch (New York, N. Y.): I would like to ask Dr. Harrison whether the internists at his hospital have made requests to obtain needle biopsies of the kidneys.

Dr. Kendall Emerson (Boston, Mass.): I'm afraid I can't say much about differential salt excretion, simply because they haven't been measured enough, to my knowledge, to be used as a valid test of renal function. Certainly it is something that ought to be studied more intensively. Perhaps some others have studied it more than we have.

One might expect that it would vary with the type of renal lesion. If one had a lesion involving a good deal of tubular damage, it's possible that you could get a salt-losing nephritis on one side. I have never seen that, and it would be interesting to know whether that ever happens. I'm afraid we haven't been able to use it as a useful tool as yet.

In regard to nephrectomy versus adrenalectomy for the cure of hypertension, if we could be sure that the hypertension was renal in origin, as we have been talking about this morning, one would certainly far prefer nephrectomy. I

think we have found that adrenalectomy is rather unsatisfactory in treating renal hypertension.

Perhaps Dr. Harrison will say more about this, but in order to maintain the patient in anywhere near normal health, one has to feed him such amounts of adrenal cortical replacement therapy that he very nearly returns to the preceding level of hypertension.

In other words, you cannot adjust the dose of desoxycorticosterone to keep him at normotensive levels. If you do, he's very unhappy, miserable, weak and tired, and can't do much.

The tendency is to give these patients enough replacement therapy so that they feel well, and when they feel well their pressures are pretty nearly back to where they were beforehand, so that has been the main difficulty with adrenalectomy. In some of the earlier cases or less severe cases, adrenalectomy has been successful, and patients can be kept in pretty good general condition with substitution therapy, and still maintain reasonably normal blood pressures.

DR. HARTWELL HARRISON (Boston, Mass.): In answer to Dr. Davis' question, one twin had scarlet fever and the other one didn't, which accounts for why one had glomerulonephritis and one did not.

In answer to the question regarding renal needle biopsy I would say that this is a controversial subject. We have done a small number of these for the medical service in studying patients with severe advanced renal failure. The purpose of the procedure is to determine whether or not reversible renal disease is present and therefore if it is worth while to proceed with repeated dialysis with the artificial kidney in prolonging life. In general I do not approve of needle biopsies and believe that an open adequate procedure should be carried out in obtaining the most accurate information. The hazard of needle biopsy is illustrated in a patient whom I thought should not have a needle biopsy because of severe hypertension. A resident, nevertheless, did a needle biopsy and inadvertently hit the renal artery. The patient required six transfusions of blood and the necessity for operation with suturing of the injured vessel.

In answer to the question on salt excretion we do have some information with reference to the obstructed kidney. Following the relief of obstruction marked sodium chloride diuresis has been demonstrated during the recovery period of the kidney. This is illustrated by the accompanying slide which shows a man, age 76, with prostatic obstruction, who, after being placed on constant drainage, excreted 8 liters of urine the first day containing 270 milliequivalents of sodium and on the second day excreted 11 liters of urine with an output of more than 300 milliequivalents of sodium. In one week sodium excretion has been reduced to normal limits and during that time there was a striking fall in blood pressure. Such a tremendous sodium excretion demands adequate replacement to prevent hyponatremia. An adequate sodium intake under these circumstances prevents the necessity for an excessive replacement of water.

I had planned, Dr. Heckel, to show a few illustrations with reference to homologous transplantation of the human kidney, but I doubt if there is enough time.

While the slides are being organized I would like to answer the question with regard to adrenalectomy in hypertension. This procedure is applicable to only a rare patient with malignant hypertension. Six of our original 30 cases are now living more than five years, and have shown definite improvement. Those who had renal failure did very poorly. Those who did well were patients with congestive failure that had not responded to medical therapy, and yet they still had fairly good renal function. The improvement was judged to be on the basis of a sodium and water diuresis pursuant to total adrenalectomy.

At the Peter Bent Brigham Hospital we have done fifteen homologous transplantations of the human kidney. Twelve of these were placed on the thigh, and have been reported by Dr. David Hume and associates. One of these patients lived for 6 months with good renal function from the transplant and marked clinical improvement. Dr. Hume wrapped this kidney in a polyethylene film which protected it for a period of time from the antigen-antibody reaction, but finally pyelonephritis supervened and this transplant also failed.

Three transplants in identical twins have been done by Dr. Joseph Murray and myself.

When we were confronted with renal failure in one of identical twins, we decided that the ureter should be transplanted into the bladder in order to have the best physiological arrangement, and it seemed that the right lower quadrant was the ideal place for the kidney in the retroperitoneum, close to the bladder. This is illustrated in the accompanying slide.

(Slide) Here you see the inguinal scar overlying the transplanted kidney and here you see the excretion of indigo carmine from the transplant and above the rubber catheter emerging from the cystostomy scar of the bladder.

(Slide) This is an excretory urogram 6 months later. The function of the kidney is good and we must remember not to be too alarmed about the ureteral dilatation, because this is a completely denervated kidney, and there is no peristalsis.

(Slide) Four and six months after the transplant the left and right kidneys respectively, were removed. They were the site of chronic glomerulonephritis and one weighed 45 grams and the other 35 grams. This excretory urogram was made six months afterwards and still shows excellent function. The next slide shows the patient 6 months after operation. He has gained 40 pounds, has put on a great deal of muscle and is quite well. Recently he was married to one of our best surgical nurses. The next slide shows an excretory urogram 18 months after the transplant still showing good function and no progress in the dilatation of the ureter. Electrolyte, protein and water balance are all normal.

(Slide) This is a different problem. This patient had chronic suppurative pyelonephritis with renal failure at the age of 42. He received a kidney transplanted from his identical twin, and this was placed in the right lower quadrant. Unfortunately, a ureteral fistula developed and this is illustrated in the next slide wherein the fistula's tract has been injected with iodocholorol. The course of the ureter up to the renal pelvis is shown as well as the ureteral fistula. The fistula occurred at the point where the spermatic cord crossed the transplanted ureter. Because of this fistula, a nephrostomy was done and a polyvinyl catheter inserted

into the renal pelvis. This kidney is functioning normally and the patient's protein and electrolyte balance are normal.

(Slide) This shows the cardiac silhouette before and 3 months after the transplant. The patient still has his nephrostomy tube and we are planning to connect his renal pelvis to his bladder by means of a ureter made from a flap of bladder. At the present the patient is at his home in Washington. The cardiac size was plus 72 per cent and the transplant has been diminished to plus 10 per cent at the present time. The patient is well and in each of these cases the blood urea nitrogen has been reduced from over 200 to normal and the electrolyte balance is normal.

MANAGEMENT OF THE SEVERED URETER

FRANK C. HAMM AND SIDNEY R. WEINBERG

From the Department of Surgery, Division of Urology State University of New York, College of Medicine at New York City and Kings County Hospital, Brooklyn 3, N. Y.

Because of its sheltered anatomic position, rarely is the ureter injured by external blunt trauma. Sharp instruments or penetrating missiles can perforate or completely sever it. More frequently, injury results from extensive surgical procedures, such as radical hysterectomy. An actual perforation of the ureter is not required, ureterovaginal fistula has followed extensive damage to the adventitia with impairment of its blood supply. Such unfortunate results are not uncommon; Masterson[1] reported 11 instances of ureterovaginal fistulas following 105 radical hysterectomies with lymph node dissection. Trauma to the ureter has followed abdominoperineal resection for carcinoma of the lower sigmoid and rectum. Also, intrinsic disease of the ureter, such as tumor or a retrovocaval position, may require anastomosis of the severed ends.

The results of end-to-end anastomosis of the ureter, as with other small tube-like structures, have not been uniformly satisfactory. Thomas D. Moore,[2] probably the most outspoken in this respect, states, "through the years much experimental work has been done and numerous methods of performing end-to-end and end-in-end repair of the ureter have been described, the immediate results of which are often most encouraging; unfortunately, however, in the majority of cases, stricture of the site is almost inevitable."

The variety of techniques recommended is also evidence enough that no method has been very successful (fig. 1).[3] Arthur Cathro,[4] in an operation for retrocaval ureter, chose to divide the vena cava and reanastomose it rather than divide the ureter. He also analyzed 18 reports of end-to-end anastomosis of the ureter (for retrocaval ureter) reported in the literature and he found that only four of the 18 patients obtained satisfactory results. Nor has experimental work on animals yielded good results. A summary of recent work concerning transection and surgical repair in dogs is included in table 1.

We believe the outlook for restoring the continuity of the ureter need not be so gloomy providing certain principles are observed.[5] At least it can be tried with a reasonable chance of success. Nephrectomy may be done at a later date if necessary.

Acknowledgement is made to the Winthrop Laboratories for their generous supply of hypaque solution, the contrast medium used to obtain the canine intravenous urograms.

[1] Masterson, J. G.: Analysis of 105 radical hysterectomies and pelvic lymph node dissections performed in treatment of uterine malignancy. In press, Am. J. Obst. & Gynec.

[2] Moore, T. D.: Surgery of the Ureter. In Urology, edited by Campbell. Philadelphia: W. B. Saunders Co., 1954, vol. 3, sect. 15, chapt. 4, p. 1864.

[3] Textbook of Genito-Urinary Surgery, edited by H. P. Winsbury-White. Baltimore: Williams & Wilkins, 1948, p. 206.

[4] Cathro, A. J.: Section of inferior vena cava for retrocaval ureter: A new method of treatment. J. Urol., **67:** 464–475, 1952.

[5] Hamm, F. C. and Weinberg, S. R.: Experimental studies of regeneration of ureter without intubation. J. Urol., **75:** 43–51, 1956.

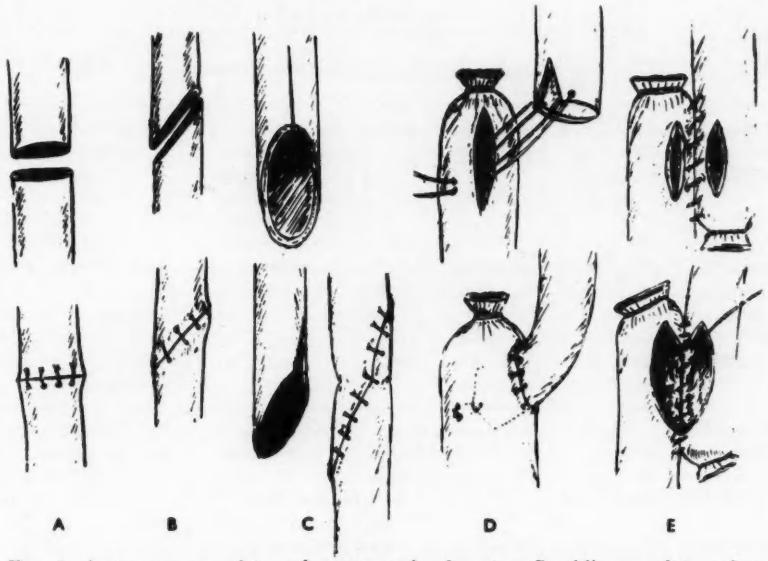

FIG. 1. *A*, transverse end-to-end anastomosis of ureter. *B*, oblique end-to-end anastomosis of ureter. *C*, oblique end-to-end anastomosis with longitudinal split of obtuse side. *D*, end-to-end anastomosis with longitudinal split of upper segment on one side. *E*, side-to-side anastomosis of ureter. From TEXTBOOK OF GENITO-URINARY SURGERY, edited by H. P. Winsbury-White. Baltimore: Williams and Wilkins, 1948.

In the event that the ureter is transected, a serious interference with the physiology results, peristaltic waves originating in the proximal segment proceed to the severed level and stop, nor will they traverse the recently sutured ends. In the severed ureter a peristaltic wave may therefore encounter a contracted segment below the point of anastomosis. A dilatation of the proximal segment is the rule for the first week or two, following end-to-end anastomosis, without diversion of the urinary stream above the site. However, after healing without cicatrix is complete, synchronous peristalsis is resumed.

Dilatation of the proximal segment means increased pressure and under these circumstances it is unlikely that any type of suture will result in a watertight anastomosis. Therefore we have not attempted to effect a watertight closure, but have used fine atraumatic everting interrupted mattress sutures designed to approximate the mucous membrane primarily and not allow fibrous tissue to interpose between the joining epithelium. Pressure on the suture line is relieved by making a linear incision well above the site of anastomosis (fig. 2); drainage is provided by rubber tissue for a minimum period of 9 days or until urinary drainage ceases. Our experimental work emphasizes the importance of maintaining adequate drainage.

Another important principle to be observed in restoring the continuity of a small tube-like structure, is a type of anastomosis that will increase the circum-

TABLE 1

Name of Investigator and Reference	No. of Dogs Used	Procedure and location of Anastomosis	Type of Anastomosis	Results
Marion, H. J. d'urol., **27:** 273, 1929	8	Junction of lower and mid-third.	End-to-end, 4 denuded; 4, hot needle to mucosa.	All strictured at point of suture
Bump, W. S. and Crowe, S. Surg., Gynec. & Obst., **49:** 346–351, 1929	26	Catheters removed in 8–14 days. Catheters for diversion of urine. Mid-ureter anastomosis	Transverse end-to-end.	6 died of post-op. infection. 6 successful with good condition of kidney and normal histologic appearance of anastomosis.
Iselin, M. Surg., Gynec. & Obst., **49:** 503–509, 1929	12	Accompaning pyelostomy. Solid bougie splinting ofureter.	Transverse end-to-end.	5 died of peritonitis, infection always present. Peristalsis observed to be very slow.
Hryntschak, W. Ztschr. f. urol. chir., **42:** 268, 1936		Nephrostomy used and ureters splinted.	Transverse-to-end.	Histologic examination: fibrosis at site. Majority of dogs died of peritonitis or urinary extravasation. 2 had good functional results, except for hypertrophy of ureter.
Wildbolz, E. Ztschr. f. urol. chir., **42:** 56, 1936.	6	Reanastomosis with circular continuous suture.	Transverse end-to-end.	Good results in seen 2 years later. Believe good results a matter of technique, but dilatation noted above suture line.
Kramer, S. E. Surg., Gynec. & Obst., **46:** 217–220, 1928	3	Mid-ureter, catheters to pelvis and across anastomosis	Transverse end-to-end.	All had stricture at site of anastomosis.
Davalos, A. J. Urol., **58:** 22–27, 1947	18	Mid-ureter	Continuous everting mattress suture.	Good results in 1 dog 7 months postoperatively

TABLE 1. *Continued*

Name of Investigator and Reference	No. of Dogs Used	Location of Anastomosis	Type of Anastomosis	Results
Sutherland, C. G., Brown, W. E., Atkinson, J. C. and Birmingham, R. T. South. Med. J., **47:** 525–530, 1954	6	1″ of lower third of ureter resected, polyethylene catheter bridged the gap and passed into bladder.	No suture	All strictured after gap in ureter healed by filling in with fibrous tissue.
	4	Lower third severed transversely and ureter intubated with polyethylene catheter.	End-to-end anastomosis.	Catheter removed 4th day. Result in 10 days, incomplete healing on 38th day. Stricture mild to complete.
Weisman, J. L. Brit. J. Urol., **6:** 11–26, 1934	9	Extraperitoneal anastomosis done close to insertion of ureter into bladder, No. 4 or 5 F urethral catheter as splints.	Transverse incision, end-to-end.	5 dogs had good lumen; stricture formation and urinary extravasation in 4 dogs.

FIG. 2. Anastomosis with everting mattress stitch

ference. A Z type of anastomosis has been advocated by Holman (fig. 3),[6] and Anderson and Hynes (fig. 4)[7] have devised a novel method of anastomosis. The simplest and most satisfactory method of increasing the diameter of the ureter

[6] Holman, E. and Hahn, R.: Application of Z-plasty technique to hollow cylinder anastomoses. Ann. Surg., **138:** 344–349, 1953.

[7] Anderson, J. D. and Hynes, W.: Retrocaval ureter. Brit. J. Urol., **21:** 209–214, 1949.

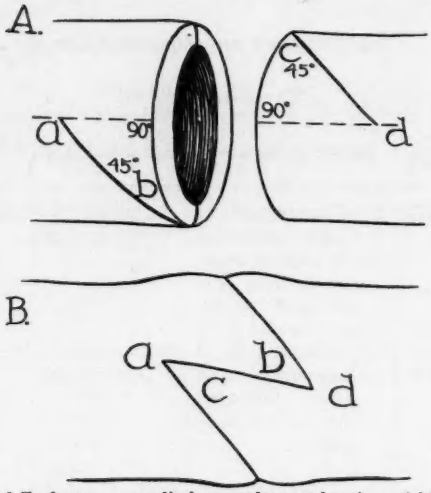

FIG. 3. Principle of Z-plasty as applied to end-to-end union of blood vessels: parallel incisions *a b* and *c d* are made permitting approximation of *a* and *c*, *b* and *d*, with definite increase in circumference at site of anastomosis. (After Holman.[6])

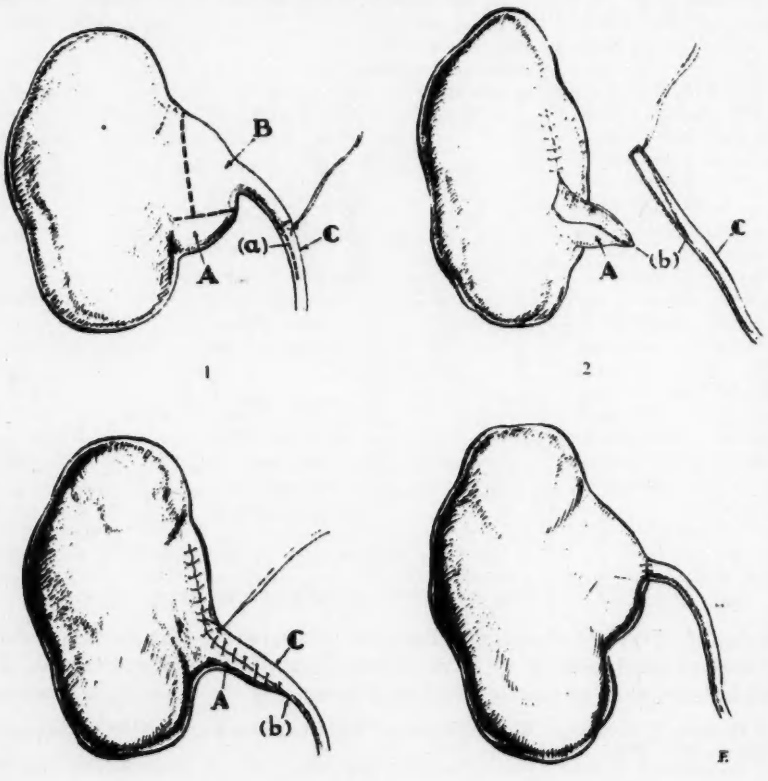

FIG. 4. *1*, *2*, *3*, Type of ureteropelvic anastomosis, as advocated by Anderson and Hynes.[7] *4*, Type of anastomosis that is prone to produce circular scar and subsequent stricture formation.

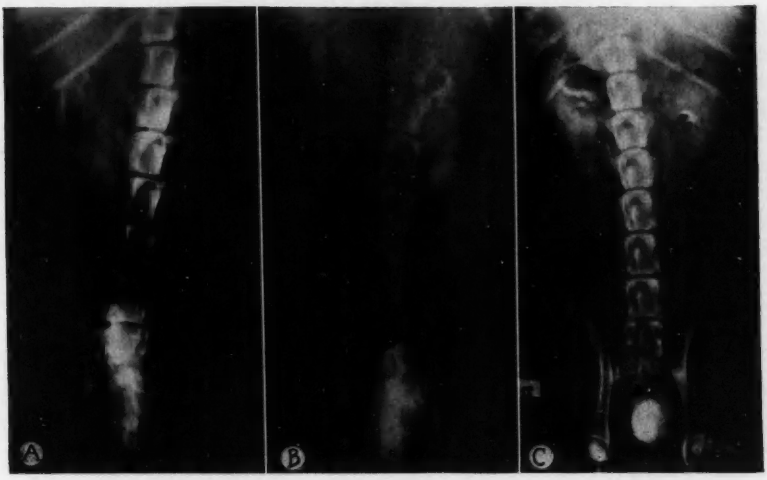

FIG. 5. *A*, dog No. 349. Bilateral ureteroureteral anastomosis. Right visible, 10 months postoperatively; left, 8 months postoperatively.
B, dog No. 525. Solitary kidney, 3 months postoperatively.
C, dog No. 554. Right anastomosis 5 months postoperatively.

is simply to incise each end for a distance of about one centimeter, as described by Nesbit[8] in his ureterointestinal anastomosis and join the spatulated ends with fine everting chromic catgut. No splinting tube or catheter has been required.

RESULTS

Clinical. Patients who require this type of surgery are seen infrequently; only one human subject, a man (M.S. 44 years, Kings County Hospital No. 88,986) had a repair of a ureter with spatulated end-to-end anastomosis. His ureter was severed while undergoing ligation of inferior vena cava in April 1955, on the general surgical service, University Division, Kings County Hospital. No diversion of the urine above the site of the anastomosis was done. Some dilatation of the proximal segment was present for over six weeks. A urogram taken during the twelfth postoperative week indicated that the dilatation had subsided and the pyelogram was almost normal. He has been followed for 13 months with no symptoms referable to his right kidney and no instrumentation has been required.

Experimental. Twenty anastomoses were done in 16 dogs; 4 dogs had both ureters divided and joined. Of the 16 dogs, four died of distemper in from two to six days postoperatively including one dog with bilateral anastomosis. Autopsies were performed on all four; the site of anastomosis was satisfactory. Of the remaining 12 dogs, five died of urinary extravasation as a result of pulling or chewing out the drain before healing had taken place. In four of the 5 dogs, the drains were chewed out on or before the sixth day; in the fifth, it was removed on the ninth day postoperatively and the dog died on the eleventh day.

[8] Nesbit, R. M.: Ureterosigmoid anastomosis by direct elliptical connection; preliminary report. Univ. Hosp. Bull., Ann Arbor, **14**: 45, 1948.

This dog had a bilateral anastomosis; at autopsy a calculus and obstruction were noted in the right kidney (operated upon 3 months previously). Autopsy on the other dogs in this group indicated that they died of urinary extravasation and infection.

The 7 dogs remaining are still alive from 2 to 11 months postoperatively. Two had both sides operated on, making a total of nine anastomoses (fig. 5, *A*). In one animal the first anastomosis was a failure resulting in a pyonephrotic kidney. This was removed and the solitary ureter was severed and anastomosed. This dog is still alive and well (fig. 5, *B*). A second obtained a poor result but retains good function and appears healthy. The remaining seven anastomoses in six dogs appear to be functioning well and the dogs are healthy (fig. 5, *C*).

The results in the human subjects should be better than those in the dog.

The importance of maintaining adequate drainage until the ureter is healed cannot be too strongly emphasized. In those animals where the drain came out prematurely with marked fibrosis of the ureteral tissues, constriction of the ureter or death occurred rapidly due to wide extravasation.

SUMMARY

Satisfactory results were obtained in seven of 9 operations on 7 dogs, where the ureter was severed and reanastomosed using a vertical slit in each end to produce a spatulated effect, thereby increasing the caliber of the ureter at site of anastomosis. The suture was a fine chromic everting stitch. The urine was diverted by a linear incision made well above the site of anastomosis; no splinting catheter was used.

We feel safe in recommending this operation, although it has only been used in 1 patient. Here, the technique of anastomosing the spatulated ends of the ureter was used without the ureterotomy above the site of anastomosis. He is living 13 months without complaints referable to his kidney; ureteral dilatation or instrumentation has not been required.

A NEW OPERATION FOR URETERAL ECTOPIA: CASE REPORT

THOMAS E. GIBSON

A review of the literature in 1949 by Burford, Glenn, and Burford[1] revealed that 425 cases of ureteral ectopia had been reported. To report an additional case of a condition which has been so thoroughly covered would be needlessly repetitious were it not possible to contribute a new note to some phase of the problem. It is hoped that the surgical management of the case herein reported may occasionally find useful application.

CASE REPORT

A 17-year old girl gave a history of incontinence since birth. Urological studies at the age of 2, 9, 11, 15 and 17 years had failed to elucidate the cause. She came to my office with a set of excretory urograms which appeared normal (fig. 1, *A*). Her incontinence was worse in the daytime than at night. She and her parents were becoming desperate because she was soon to graduate from high school and wished to pursue a nursing career. Suspecting an ectopic ureteral orifice from the history, my first procedure was to carefully inspect the vulva and at the same time make sudden pressure on the lower abdomen over the bladder region. This caused a spurt of clear urine to come from a small hidden opening in the vestibule between the urethra and vagina. A 6F olive-tip ureteral catheter was passed into this opening as far as it would go (4–5 cm.) and injected with neo-iopax revealing a dilated ureter extending upward toward the right kidney (fig. 1, *B*). Even with forcible injection, it was not possible to fill it above its mid-portion. The lower part of this anomalous ureter apparently terminated in a Gärtner's duct. Here, there were associated diverticula and sacculations resembling somewhat the morphology of a seminal vesicle (fig. 1, *B*).* From a knowledge of embryological developmental anomalies, the natural assumption was that we were dealing with a supernumerary ectopic ureter leading to the upper pole of a double right kidney, although the excretory urogram gave no intimation that such was the case. The right kidney was exposed through the usual right flank incision and the diagnosis was confirmed as shown in the composite drawing (fig. 2). Our intended plan of attack was to perform a right heminephrectomy and remove as much of the ureter as possible through this incision. However, this proved to be impractical for two reasons. First, the kidney resembled a normal healthy single organ and, second, the renal pedicle was anomalous, entering the kidney near the upper pole so that a partial nephrectomy was not feasible. A total nephrectomy was then considered but rejected because the idea of re-

[1] Burford, C. E., Glenn, J. E. and Burford, E. H.: Ureteral ectopia: A review of the literature and 2 case reports. J. Urol., **62:** 211–218, 1949.

* As early as 1882, Kocks[2] stated that the paravaginal portion of the wolffian duct persists in 80 per cent of women. He stated that from the distal end there develops occasionally an outgrowth in the form of a sacculated diverticulum which is known as "Schüller's gland", and it is the homologue of the seminal vesicle

[2] Kocks, J.: Ueber die Gartner'schen Gange beim Weibe. Arch. f. Gynakol., **20:** 487–491, 1882.

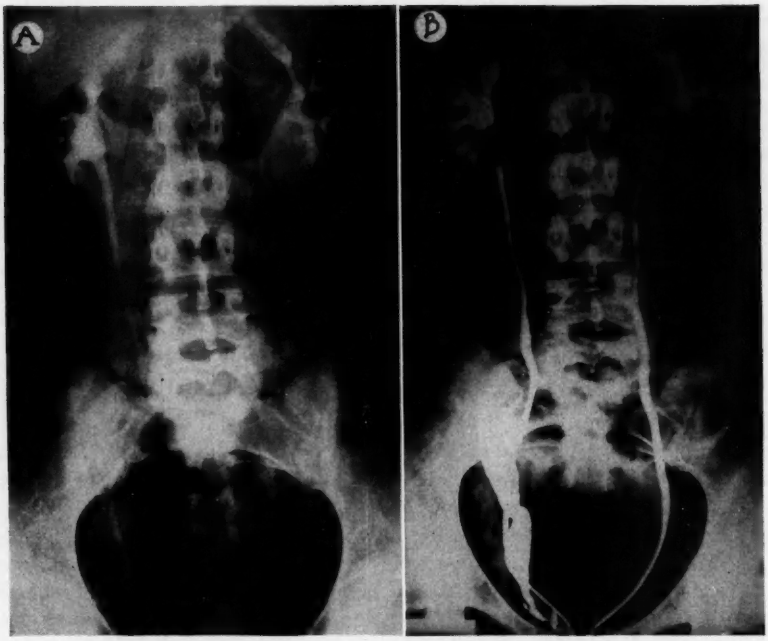

FIG. 1. *A*, excretory urogram reveals apparently normal upper urinary tract, although on right side there exists a double kidney with complete reduplication of ureter and ectopic ureteral orifice opening in vulva between orifices of urethra and vagina.

B, ectopic ureteral orifice opening in vulva was revealed by making sudden pressure over bladder region. This caused a jet of clear water to spurt from a small, almost invisible orifice situated between the urethral and vaginal orifices. A 6F ureteral catheter could be passed about 5 cm. Forcible injection of neo-iopex outlined a greatly dilated tube extending upward toward right kidney. It was impossible to inject the ectopic ureter in its upper portion. It apparently opened below in a vestigial Gärtner's duct containing sacculations or diverticula (Schüller's gland.)

moving a normal kidney was repellent. Therefore, after excision of as much of the ectopic ureter as could be reached, the upper pelvis was anastomosed to the lower pelvis as shown in figure 3. The patient had a smooth convalescence and was discharged from the hospital on the tenth postoperative day. A retrograde pyelogram 3 months later showed a satisfactory result (fig. 4). The patient has remained dry and symptom-free now for more than a year, and both patient and parents are extremely happy over the result.

COMMENT

One may wonder why such a comparatively simple solution to the problem of supernumerary ectopic ureter has not been utilized in the past. However, upon reviewing the literature it soon becomes evident that such treatment is not feasible in most cases for obvious reasons. Usually the ectopic ureteral orifice leads to a tremendously dilated ureter capped by a segment of kidney that is not only chronically infected, but has also undergone hydronephrotic atrophy so

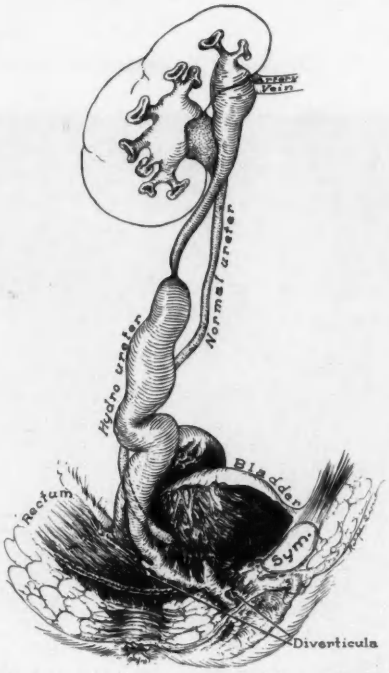

FIG. 2. Composite sketch of findings as revealed by pyelography and surgical exploration. Ectopic ureteral orifice opening in vestibule between urethra and vagina and arising from upper pole of kidney.

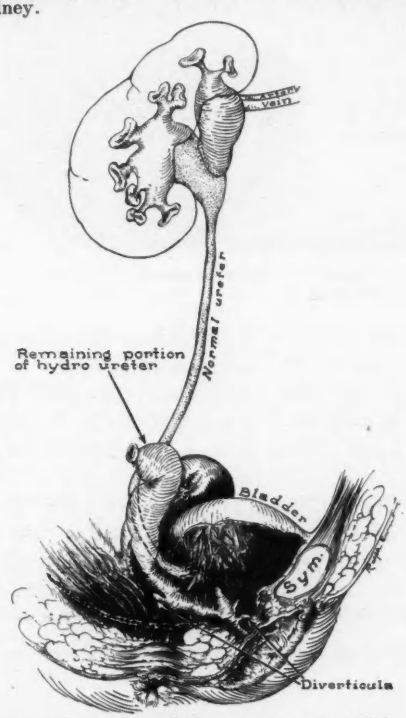

FIG. 3. Because of normal appearing kidney and renal pedicle that entered hilus near upper pole, upper pelvis was anastomosed to lower pelvis and lumbar portion of ectopic ureter removed.

FIG. 4. Retrograde pyelogram 3 months postoperatively shows satisfactory result. Patient has had no further symptoms.

that it is functionally worthless. In addition, the renal pedicle is usually so situated that heminephrectomy is comparatively easy.

In a series of some 40 cases, Campbell's[3] treatment consisted routinely of heminephrectomy and removal of as much of the dilated ureter as could be comfortably reached through a flank incision. The terminal segment of ureter was left behind and does not appear to have been a source of subsequent morbidity. Less favored procedures have been: 1) partial removal of the ureter with ligation rather than heminephrectomy, 2) ureterocystostomy, 3) excision of the entire ureter with heminephrectomy, and 4) in the milder forms of ectopia in which the ureter opens in the urethra, the orifice has been incised backward so as to open in the bladder thereby becoming subject to sphincter control. The latter

[3] Campbell, M. F.: Urology. Philadelphia: W. B. Saunders Co., 1954, vol. 1, pp. 314–324.

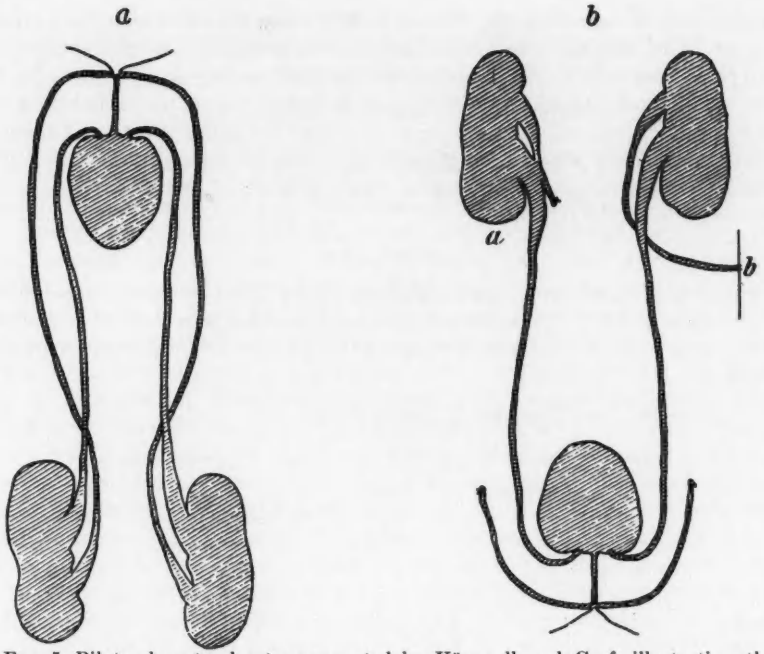

FIG. 5. Bilateral ureteral ectopy reported by Kümmell and Graf, illustrating their method of treatment.

procedure is mentioned by Kelly and Burnam[4] as having been practiced by Hunner fifty years ago. The other procedures above mentioned are obviously more hazardous than that recommended by Campbell.

Search of the literature has revealed an interesting case report by Kümmell and Graf[5] of a fifteen-year-old girl with four ureters, two opening normally in the bladder and two opening in the vagina. On the right side anastomosis of the two pelves was done (fig. 5) and later the left ectopic ureter was treated by cutaneous ureterostomy. Thom (1928) in a review of 186 cases cites 1 instance of anastomosis between the two pelves of a double kidney. Eisendrath (1938) in a review of 255 cases cites 1 case by Haselhorst in which the ectopic ureter was ligated and anastomosed to its fellow on the same side.

Aside from cases with ectopic ureteral orifices, there have been several instances of successful anastomosis of one ureter to another, either homolaterally or contralaterally. In a recent personal communication, Deming cites 2 cases of highly malignant bladder tumors in which he successfully anastomosed the ureter on one side to its mate on the opposite side. The first successful anastomosis in the living human of a ureter on one side to its mate on the opposite side was reported before this Association by Higgins in 1934 under the term, "Trans-

[4] Kelly, H. A. and Burnam, C. F.: Diseases of the Kidneys, Ureters and Bladder. New York: D. Appleton & Co., 1914, vol. 2, pp. 34–341.

[5] Kümmell, H. and Graf, H.: Handbuch der Praktischen Chirurgie, 5th ed., vol. 4, pp. 385–6. (Garre, Kuttner und Lexer).

uretero-ureteral anastomosis." Moore in 1948 collected eight such cases including one of his own, all successfully done with no mortality. Moore's comprehensive paper also includes the personal report of a successful operation, done for the first time, consisting of transureteropyelostomy in which the ureter of a left ectopic kidney was anastomosed to the pelvis of the opposite ectopic kidney.

Such procedures would be preferable to cutaneous ureterostomy or ureterointestinal implantation in cases where transplantation of one ureter has become necessary.

CONCLUSION

In supernumerary ectopic ureter, partial excision of the ureter with anastomosis of the upper pelvis to the lower pelvis is recommended provided the upper pole of the double kidney has not been destroyed by infection and hydronephrotic atrophy.

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A CLINICOPATHOLOGIC STUDY OF URETEROPELVIC OBSTRUCTIONS

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Interest in ureteropelvic obstruction was stimulated in 1937 when it was noted that interruption of an aberrant renal vessel, that seemingly was obstructing the ureter, was not necessarily followed by a recession of the associated pyelectasis. Furthermore, a normal lumen of the ureteropelvic area as determined by antegrade calibration at operation was not always indicative of functional patency any more than cystoscopic retrograde ureteral dilatation would afford anatomical or clinical improvement. In fact our experience, like that reported in the literature, made it obvious that the then practiced operative cure of pyelectasis was not always predictable. It was assumed that there were factors in operation which were not evident. Hence, this study was launched which has extended over many years because of unavoidable interruptions, investigation of false leads and the necessarily limited clinical and pathological material. To obtain material for this study it was necessary to excise the ureteropelvic junction in each instance and this necessitated ureteropelvic anastomosis which has been routinely practiced throughout this period of years with gratifying results. The evolved method of anastomosis has been described and represents a procedure whose assets embody simplicity and predictable success.

Initially it was noted that some specimens revealed a thickened muscular wall with concomitant narrowing of the ureteropelvic junction. Muscular or epithelial hyperplasia, increased elastic tissue and a preponderance of collagen were all findings seen on occasion in reviewing the surgical specimens of the ureteropelvic segment.

Owing to the inconsistency of these histologic findings longitudinal sections were substituted for the previously studied cross sections. Cutting accurate longitudinal sections of the ureteropelvic junction affords certain technical difficulties, but even so it was readily seen that for the first time the mystery of ureteropelvic junction obstruction was beginning to unfold. There were found rather frequently finger-like retrograde valvular formations which varied in number and degree. It was of interest to observe that these valvular structures appeared equally as often in instances in which there were obstructing aberrant vessels or fibrous bands as when these structures were not in evidence. Furthermore, there existed a direct relationship between the degree of valvular formation and the associated pyelectasis. The presence of these valve-like structures explained why antegrade calibration of the ureteropelvic junction was often meaningless as a method of determining the functional capacity of this lumen. This study has shown rather distinctly that pyelectasis due to ureteropelvic obstructions is most often associated with intrinsic ureteral changes and that extrinsic factors seldom play more than a minor secondary role.

FIG. 1. Longitudinal section of normal ureter

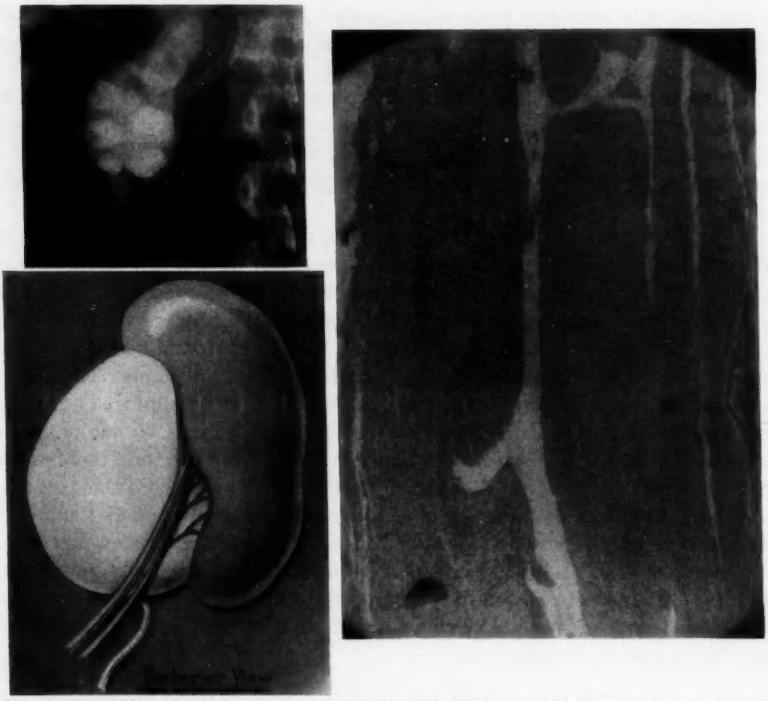

FIG. 2. No. 13937. A 44-year-old married woman with 10-year history of recurrent pyelonephritis. Vessels are of no obstructive importance.

FIG. 3. No. 140012. A 20-year-old girl with a functionless right hydronephrosis. Obstructive vessel at ureteropelvic junction is prominent.

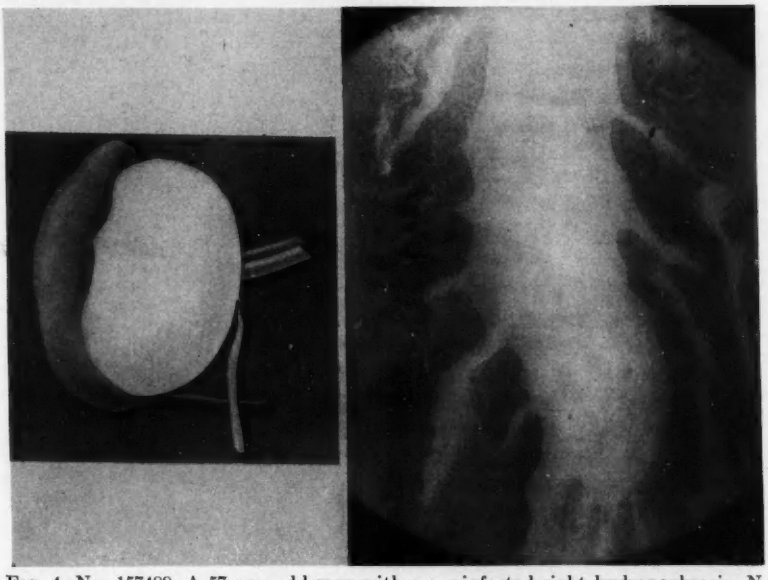

FIG. 4. No. 157488. A 57-year-old man with a noninfected right hydronephrosis. Nonobstructive aberrant vessel crosses the ureter.

In figure 1 the normal microscopic appearance of the ureteropelvic junction is demonstrated. The epithelium is relatively smooth with the ureteral wall of uniform thickness and without cellular infiltration or submucosal edema. To obtain good photomicrographs of the normal ureteropelvic area was difficult since the longitudinally cut sections would float apart on the slide so that both walls of the specimen could not be seen in the same field of the microscope.

In figure 2 the pyelogram demonstrates the degree of hydronephrosis. The drawing of the operative findings shows little if any evidence of ureteral obstruction by the abnormal course of the renal pedicle. It is true that the pedicle seems to indent the pyelectatic renal pelvis, but ureteral compression was not evident at the time of pyeloplasty. The photomicrograph of the ureteropelvic junction demonstrates the large valve-like structure (the tip of which was broken in slide preparation) pointing (upwards) toward the renal pelvis. On the opposite side near the top of the photomicrograph there can be seen the base of another valve. In the midportion of this photograph is seen a valvular structure which too was quite obstructive as the several slides were reviewed. The rather marked inflam-

FIG. 5. No. 371333. A 47-year-old housewife with pyuria and nephrolithiasis. No aberrant vessels or bands.

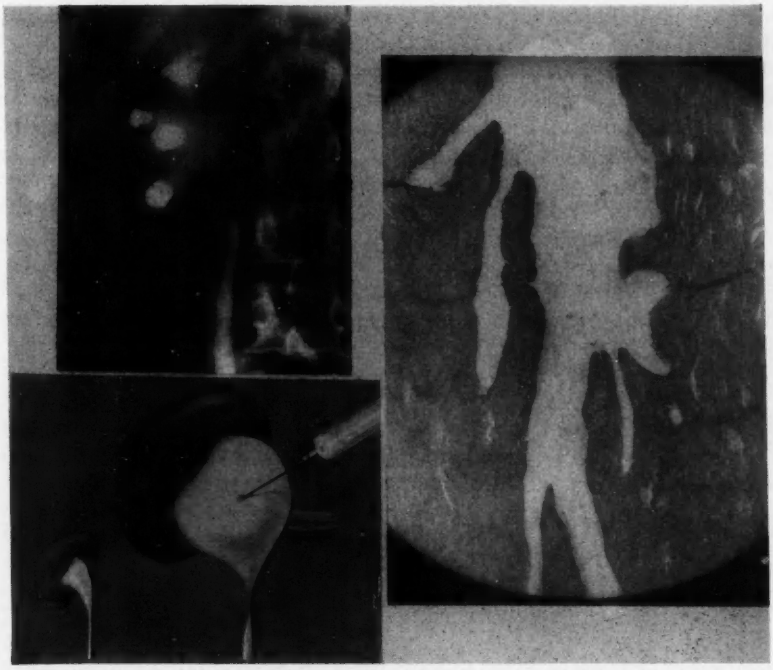

FIG. 6. No. 152572. A 27-year-old housewife with right pyelonephritis and hydronephrosis. Intermittent ureteropelvic obstruction unrelated to aberrant vessels or bands and nephroptosis.

matory infiltration is due to this patient's prolonged recurrent renal infection.

Figure 3 demonstrates a marked functionless hydronephrosis in a 20-year-old girl. In this instance the aberrant vessel seemingly obstructed the ureter. The photomicrograph demonstrates striking ureteropelvic valves which most graphically bear witness to the factor of intrinsic obstruction. Here again there is marked submucosal cellular infiltration and edema since pyelonephritis was the prominent symptom.

Figure 4 presents the findings in a 57-year-old man who suffered with "lumbago" for years. The pyelogram was virtually identical with that of figure 3. At surgery a high insertion of the ureter was found and the aberrant vessel was of no obstructive importance. The photomicrograph shows a multiplicity of ureteral valves projecting toward the renal pelvis with minimal inflammatory reaction and only moderate submucosal edema.

Figure 5 demonstrates the findings in a patient with back pain and a calyceal stone. The ureteropelvic obstruction found on urography occasioned the resection of the ureteropelvic junction at the time of pyelolithotomy. The accompanying photomicrograph of the ureteropelvic junction demonstrates a singular small valvular structure which was rather distinct in reviewing the many sec-

tions through this area, but here we have epithelial hyperplasia as the primary cause of obstruction.

Figure 6 presents the findings in a most interesting patient. A 27-year-old housewife was admitted because of repeated episodes of undiagnosed fever and pain in the right flank. The urine from the right kidney was heavily infected. A ureteropelvic obstruction was evident in the urogram, but the cause of the moderate hydroureter was unexplained and incidentally disappeared postoperatively. At surgery, when the kidney was exposed, it was somewhat disconcerting to find a normal kidney with no evidence of pyelectasis, as shown in the small insert. However, when the renal pelvis was injected with saline there appeared a most prominent ureteropelvic obstruction and marked pyelectasis which would not drain into the ureter even with manual compression of the pelvis. The multiple valve-like formations in the accompanying photomicrograph are evident.

SUMMARY

The subject of intrinsic ureteropelvic obstructions is discussed. The common finding of retrograde valve-like formations is presented and their appearance is unrelated to secondary extrinsic factors of ureteral compression.

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REFERENCE

LICH, R., JR., MAURER, J. E. AND BARNES, M. L.: Pyelectasis. J. Urol., **75**: 12–16, 1956.

THE RESULTS OF Y PLASTY AFTER FIVE TO TWENTY FOUR YEARS: A REVIEW OF SEVENTY THREE OPERATIONS

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While intermittent hydronephrosis from obstruction at the ureteropelvic junction is said by Troup to have been recognized as early as 1672, over two hundred years elapsed before Trendelenburg first tried to correct it surgically in 1886. Causative lesions may be congenital or acquired: included are strictures, accessory vessels to the lower pole, fascial sheets and bands (fig. 1); postinflammatory fibrosis external to the junction; valves as well as granulomas and polyps of the mucosa; high attachment of the ureter to the pelvis; nephroptosis (fig. 2); and neuromuscular dysfunction. Combinations of two or more of these are common. It may be that accessory vessels and ptosis are more often contributory than exciting causes, and it is uncertain whether high ureteral attachment is a cause or an effect of hydronephrosis (fig. 3). The exact nature of "neuromuscular dysfunction" is unsettled; spasm of the junction, hypotonia of the pelvis, and dysinnervation of both have been suggested as causes, but the term really means only that the ureter is normal and the pelvis dilated in the absence of demonstrable anatomical obstruction.

The disorder is usually discovered during urography done because of renal pain, or of persistent or recurrent urinary infection. The essential feature is a dilated pelvis with a normal ureter; the nature of the underlying lesion may or may not be detectable.

If pain is unmistakably renal, or if the hydronephrosis is infected, one concludes that surgical treatment is needed. If, however, the symptoms are atypical or the hydronephrosis is small, particularly in the absence of infection, additional diagnostic measures are needed. Distension of the renal pelvis through an ureteral catheter may prove the relationship between hydronephrosis and pain by reproducing the latter, but only if the patient is unaware of the purpose of the maneuver; otherwise suggestion may cause confusion. However, if the pain produced by distension differs in character and in location from that of the original complaint, it is safe to assume that the origin of the symptoms is extrarenal.

The delayed retrograde pyelogram is also valuable. If one fills the pelvis with contrast agent, removes the catheter, and has the patient walk about for ten minutes, radiography should show an empty or virtually empty pelvis. Delay in evacuation, particularly if the calyces are clubbed, strongly suggests genuine obstruction.

As Nesbit recently emphasized, a patient may have genuine renal pain, yet have a normal urogram between attacks, whereas one made during pain, either spontaneous or induced by diuresis, may disclose frank hydronephrosis.

Differential diagnosis may be difficult in a patient who complains of digestive disturbances and who proves to have hydronephrosis only after studies of the

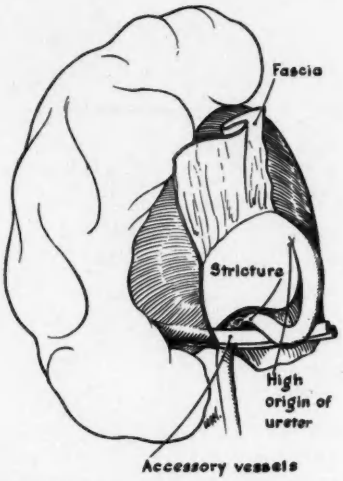

FIG. 1. Composite diagram of accessory vessels, stricture and fascial sheet in obstruction at ureteropelvic junction.

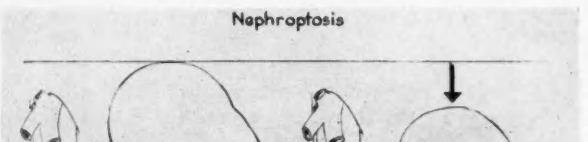

FIG. 2. Probable role of nephroptosis in ureteropelvic obstruction

gastrointestinal tract have been normal. It is tempting to advise operation in these circumstances, but one must remember that the renal lesion may have nothing to do with the complaints. Hëllstrom, Giertz, and Lindblom; O'Conor, and Gibson have concluded that certain hydronephroses may reach equilibrium and thereafter fail to progress or cause trouble. This situation may be recognized by the absence or atypical character of the symptoms, and from the fact that urograms made at fairly long intervals show no increase in the dilatation. One should be particularly skeptical of any causative relationship between digestive disturbances and small hydronephroses, while large ones may undoubtedly disturb gastrointestinal function by pressing upon adjacent organs.

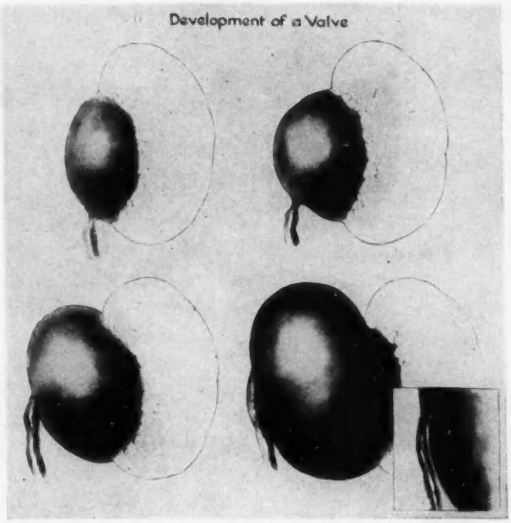

FIG. 3. Development of acquired high origin or attachment of ureter

Having ascertained that a noncalculous obstruction is causing symptoms severe enough to require surgical treatment, one must decide whether the kidney should be repaired or removed. Several factors have to be considered. First is the functional and anatomic state of the affected kidney. It has been proved that half a normal kidney, or even less if there has been opportunity for compensatory hypertrophy, can support comfortable life. This can be determined pretty accurately from excretory urography, indigo carmine excretion, and from inspection and palpation at operation. If one half of the parenchyma remains and if its color is normal, the kidney is usually worth saving. If the kidney is discolored, it may be useful to have a fast frozen section examined to avoid leaving an organ seriously damaged by infection or fibrosis. Doss has suggested that aortography be used to determine, from the blood supply, whether an organ is salvageable, but the necessary information can usually be secured without this extra procedure.

Another factor is the state of the opposite kidney, the presence in which of any disease, however mild, intensifies the need to preserve its mate. A third important consideration is the age of the patient. There is but little reason to save the kidney of an individual whose opposite organ has remained normal for 60 years if there is any doubt of the feasibility of doing so. On the other hand, the kidney of a child or young person will be exposed to the possibility of disease for so long that conservation of renal tissue is important. This attitude is re-enforced by Sargent's observation that removal of a kidney with fair function may so increase the volume of urine excreted by the other side as to convert a latent, unrecognizable noncalculous obstruction into a genuine one requiring treatment. When the obstructed kidney is a solitary one, there is no choice.

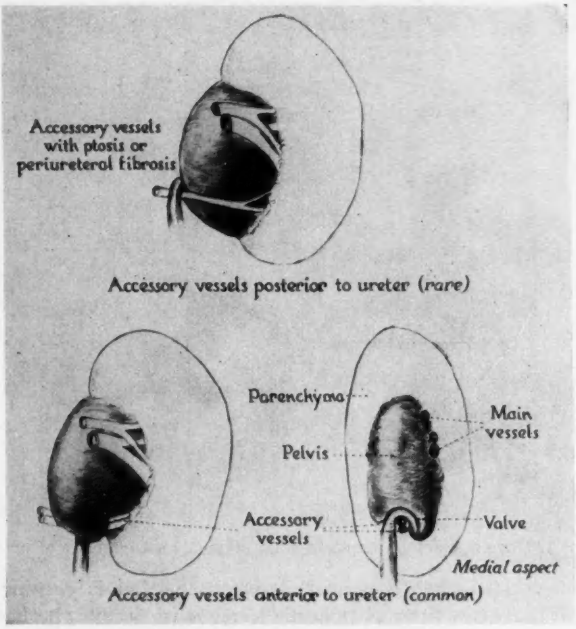

FIG. 4. Accessory vessels to lower pole of kidney

Before discussing the type of plastic operation best suited to a particular situation, it is desirable to deal with the problem of accessory vessels to the lower pole. While many experienced surgeons agree that they can cause obstruction *per se* (fig. 4) and while Quinby suggested that the pounding of an artery against the ureter could interfere with peristalsis, pathologists see at autopsy many such vessels without hydronephrosis; Bell mentions 77 examples of accessory vessels, only 20 of which were associated with hydronephrosis. Moreover, so called neuromuscular dysfunction is fairly common, and I know of no dependable method of identifying it in the presence of polar vessels. It has often been suggested that this can be determined if, after separating them from the junction, one observes the rate at which saline injected into the pelvis flows down the ureter. Unfortunately, I am never sure whether the rate is normal.

I have therefore preferred to perform a plastic upon the junction if there is any doubt whatever that the vessels cause the hydronephrosis, thus avoiding the risk of missing a functional obstruction. I realize that arguments can be presented upon the other side.

While it is generally agreed that an artery which supplies more than one fifth of the kidney should not be cut, and that veins of considerably larger size may be sacrificed, one's attitude will vary with circumstances. If the opposite kidney is abnormal or absent one will want to do the least possible damage. If the other one is normal, one may compromise a little more parenchyma with a clear con-

science. If too much tissue becomes cyanotic with temporary occlusion of the vessels, one should consider some variant of Patch's method of dividing the renal pelvis and suturing it in front of them. Since this does not obviate overlooking a coexisting functional obstruction, it seems wiser to divide the junction itself and to make a terminolateral anastomosis between ureter and pelvis in the manner of Wilhelm, Nesbit, and others (fig. 5). Young excised diamond shaped pieces from the anterior and posterior surfaces of the pelvis and sutured them so as to displace the junction downward away from the vessels. I believe that this principle

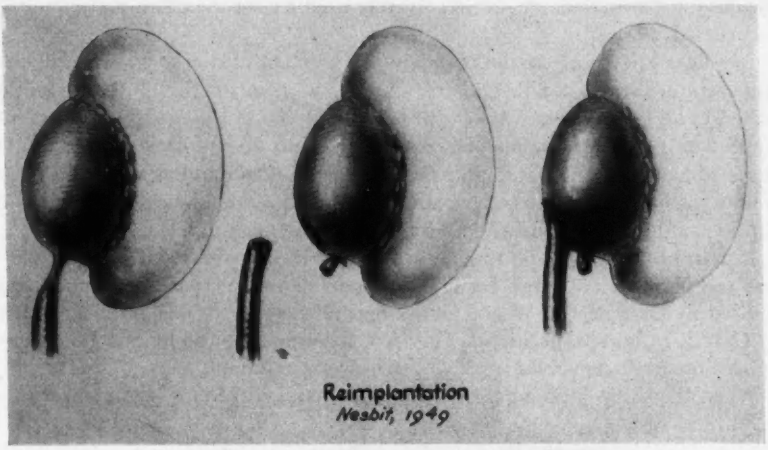

FIG. 5. Terminolateral anastomosis. (After Nesbit.)

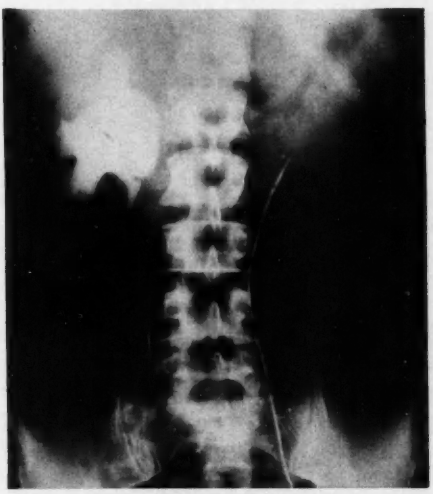

FIG. 6. Compression of renal pelvis by vessels left well above ureteropelvic junction at Y plasty.

is unsafe. I once preserved a pair of sizeable vessels after Y plasty had displaced the junction well below them, because the opposite kidney was functionless. A subsequent pyelogram made because of persistent obstruction demonstated that the vessels had indented the dilated pelvis an inch above the ureteropelvic junction; reoperation disclosed that the lumen behind them was filiform, while the junction was normal in caliber (fig. 6).

Stewart has altered the relationship between vessels and junction by approximating the poles of the kidney with the aid of capsular flaps sutured together medially with satisfactory results, but this is subject to the disadvantages already mentioned.

My own preference in the majority of instances of noncalculous obstruction has been for Foley's modification of Schwyzer's operation (fig. 7). It is admirably suited to all types except those with pelves so large as to require partial excision to prevent postoperative pooling of the urine, and those with strictures too long to be widened by any obtainable flap. It has two outstanding advantages: continuity of pelvis with ureter is maintained so that complete postoperative disruption cannot occur, and the ureteropelvic junction is made dependent.

If a stricture is too long to be corrected by the conventional Foley Y plasty, and the pelvis is not large enough to require partial excision, the modification devised by Culp and DeWeerd (and independently by Prince and Scardino and by Gordon) (fig. 8, *1*) is useful. Very few strictures are too long to be corrected by this method; the advantages of Y plasty are retained.

When the pelvis is so large as to require partial excision, a slight modification

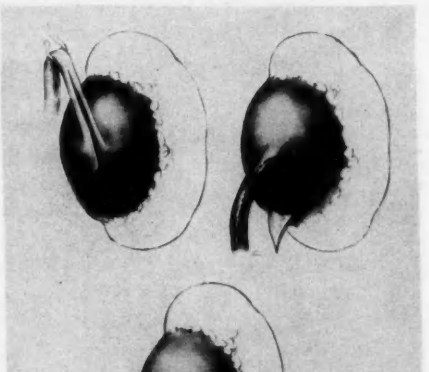

FIG. 7. Foley's Y plasty

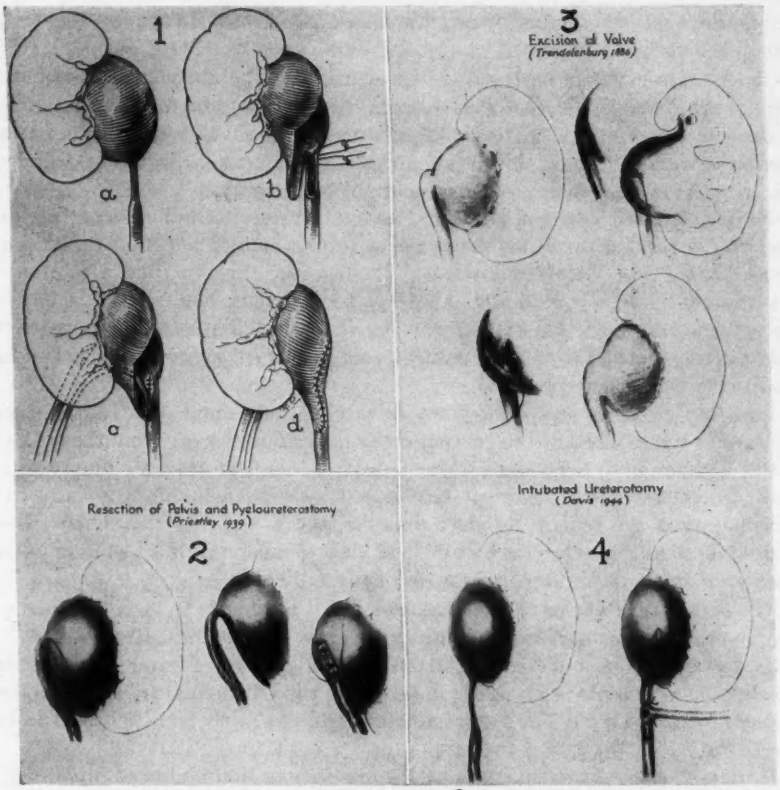

FIG. 8. *1*, Method of Culp and DeWeerd. *2*, Priestley's operation. *3*, Trendelenburg's technique. *4*, intubated ureterotomy of Davis in its early or simple form.

of Priestley's operation (fig. 8, *2*) may be considered. His original method resembles that of Trendelenburg (fig. 8, *3*) done from without instead of from within the renal pelvis. One can make the excision so as to leave a long flap at the inferior margin of the pelvis, and this can be sutured into a slit in the ureter as in Y plasty. The same result can be achieved by partial resection of the pelvis with terminolateral anastomosis of the ureter to it after closure of the resultant defect, but continuity of pelvis and ureter is not maintained.

When the stricture is long and the pelvis small (an unusual situation), Davis' intubated ureterotomy (fig. 8, *4*) is invaluable. My only patient with such a condition had had traumatic avulsion of the ureter from the pelvis of his solitary kidney, late nephrostomy, and an unsuccessful intubated ureterotomy prior to admission, and had worn a nephrostomy for 2 years. No flap could be made from the shrunken pelvis. In lesions which can be corrected by other means, I prefer to use them because it seems to me that the protracted use of an inlying catheter in the pelvis greatly increases the danger of an intractable infection, particularly

with urea splitters. Moreover, prolonged wearing of such a tube is a great nuisance for the patient.

In the rare event of destruction of a segment of the upper ureter so that it cannot reach the pelvis, the operation of Neuwirt should be remembered: anastomosis of the ureter to the lower calyx, with or without resection of the parenchyma around it. Since this is an antiperistaltic arrangement, one wonders whether use of a segment of ileum would not be preferable.

Having selected a technique suited to problem of the individual, the next question is that of diverting the urine to protect suture lines during healing. Until Hamm and Weinberg published their views, this was just a matter of nephrostomy versus pyelostomy. They maintain that catheters serve merely to convey bacteria to the kidney. Anyone who has seen lithiasis from urea-splitting bacteria ruin the end result of a meticulously performed plastic will give serious thought to their suggestions.

Both nephrostomy and pyelostomy have advantages and disadvantages. In the former the renal end of the catheter can be fixed well away from the anastomosis, insuring both adequate drainage and freedom from pressure upon suture lines; if necessary the catheter can be changed without much difficulty and without disrupting the repair. Its chief disadvantage is the fact that renal tissue injured in making it serves as an excellent culture medium, thus fostering infection; even the miracle drugs may occasionally fail here.

Pyelostomy does not have this weakness, but it is difficult to place the tube so that it drains efficiently without impinging upon suture lines. Replacement is likely to be difficult, and removal of the catheter may burst suture lines unless a Robinson catheter is used; this is more apt to slip out prematurely than is the Malecot, which I prefer. The Foley catheter requires a fairly large pelvis to drain effectively.

There is no general agreement about the necessity or desirability of "splinting" the anastomosis with a catheter or polyethylene tube except in the case of intubated ureterotomy, of which it is an essential part. From the viewpoint of Hamm and Weinberg it is objectionable, and evidence of its virtue except in the situation just noted is lacking. Priestley prefers to use a splint, and Gibson calls it indispensable except in the "double Fenger" plastic. Here the junction is slit vertically through both layers and sutured transversely. It is not clear why it is unnecessary here but vital in essentially similar operations. I suspect that the function of the splint is to prevent suturing across the lumen of the anastomosis; once the latter has been made, the catheter may be withdrawn. I must admit that, in operating for bilateral disease or upon solitary kidneys I splint the anastomosis with a T tube, which also decreases the danger of postoperative extravasation.

CLINICAL MATERIAL

The records of 77 consecutive patients subjected to 81 Y plasties (4 were bilateral) between 5 and 25 years ago have been reviewed. Ages ranged from 18 months to 59 years. Seven patients with 8 operations failed to respond to ques-

tionnaires or to return for followup, leaving 70 individuals with 73 operations for review. All of these returned questionnaires, and all but nine returned for examination.

Preoperative investigations and findings at operation disclosed the following causes of obstruction at the ureteropelvic junction:

Accessory vessels to the lower pole	17
Stricture	16
Neuromuscular dysfunction	14
Vessels and fascial sheet	12
Periureteral scar	6
Postinflammatory polyps	3
Fascial sheet, high attachment of ureter	3
Vessels and stricture	3
Vessels, stricture, and fascial sheet	3
Fascial band	3
Granuloma	1
	81

Complicating lesions present before operation included:

Stones not contributing to obstruction	6
Bilateral obstruction	4
Slight ureterectasis	3
Horseshoe kidney	3
Ectopic kidney	2
Solitary kidney (acquired)	2
	20

RESULTS

Assessment of the result of an operation like Y plasty, which is life saving only if the kidney is solitary, is not easy except in failures, and depends greatly upon the judgment of the reviewer. It is doubtful that any two urologists could review this material and arrive at the same conclusions. The criteria used in this review are: the degree of subjective relief, the state of the urine, and the findings on urography. Results are classified as excellent, good, fair, or as failures. In terms of subjective relief, "excellent" means complete disappearance of symptoms; "good", that the patient reports occasional mild discomfort on the operated side; "fair", that there has been recurrent nondisabling pain with evidence of infection; and "failure", that relief did not occur and, usually, that a second operation was necessary. While 2 patients are perfectly well after secondary operations and a third requires annual ureteral dilatations to be comfortable, these are classed as failures because the original Y plasty failed to achieve its objective.

In terms of the urine, "excellent" means clear, sterile urine; "good" refers to the presence of bacteria without pus; "fair" means that a few pus cells are present together with bacteria.

There is obviously room for quibbling in interpreting the urograms. For our purpose, an excellent urogram is one which shows no impairment of function; the size of the hydronephrosis has diminished and the calyces have returned to

normal, the ureteropelvic junction is funnel shaped, and contrast agent enters the ureter promptly. A good urogram fulfills the above criteria except that the size of the pelvis has not diminished. In a poor one, there is persistence or increase of the hydronephrosis, unaltered narrowing at the junction, delayed transit of urine down the ureter, or diminution of the renal function.

Combining these criteria, results were excellent in 44 of the 73 operations, or 60.3 per cent; they were good in 17, or 23.4 per cent; and fair in one, or 1.3 per cent. Eleven, or 15 per cent were failures.

CAUSES OF FAILURE

Several factors are likely to contribute to failure of a plastic operation upon the ureteropelvic junction. First of these is an inaccurate estimation of the relationship between the hydronephrosis and the symptoms, which is particularly likely in the patient with small hydronephrosis, so-called "reflex" gastrointestinal symptoms, and an overenthusiastic surgeon. It is obvious that widening the outlet of the kidney will not relieve symptoms unrelated to the renal lesion.

A second source of error is overestimation of the functional capacity of the diseased kidney, so that a hopelessly injured organ is "repaired." Failure may result either because residual renal tissue is so fibrotic that infection cannot be eliminated, or because the motor mechanism is so impaired (fibrosis or atony) that it cannot propel the urine satisfactorily. While the former defect can be estimated with reasonable accuracy by means of preoperative function tests and by inspection at the time of operation, supplemented perhaps by study of a fast frozen section, I know of no satisfactory method of determining the latter except by trial and error.

Many errors of technique can cause failure. Most easily avoided is the use of nonabsorbable sutures, although the relationship between foreign bodies and lithiasis is so well known that this should not occur. Neglect to reduce the size of a greatly dilated pelvis may leave such a large pool of urine that infection resists treatment. Conversely, resection of too much pelvis, accompanied by peripelvic and periureteral fibrosis may cause constriction of the ureter where it is pulled against the lower pole of the kidney; this requires intubated ureterotomy, or it may be irreparable. Leaving aberrant vessels anterior to the renal pelvis because it has been possible to anchor them well above the ureteropelvic junction may lead to obstruction of the pelvis itself, as already mentioned. Division of accessory vessels which supply an unexpectedly large part of the parenchyma may leave too little functioning tissue to be useful; theoretically at least, a clot can be propagated backward from a ligated vein to the main renal vein and cause infarction. The ligation of accessory renal arteries has been alleged to cause hypertension, but satisfactory proof is lacking.

In my experience another source of failure is the provision of inadequate diversion of the urine during healing, either by improper placement of the diverting catheter, or by inefficient anchoring so that it slips out prematurely. This is readily avoided by the exercise of care at the time; an inlying ureteral catheter may save the kidney if the tube slips out.

Occasionally, without any obvious technical fault, scarring around the junction may produce recurrent obstruction, presumably because of extravasation or postoperative infection.

The commonest single cause of failure in my own experience has been postoperative infection of the kidney with an urea splitting bacterium, usually Bacillus proteus. Since catheters for urinary diversion and splinting appear to conduct these organisms into the bladder from contaminated bedclothes (Bacillus proteus is a common inhabitant of the colon), this is a powerful argument for the omission of catheters, as suggested by Hamm and Weinberg. If they are used, one should try to prevent infection by using antibiotics wisely; it seems reasonable that lithiasis can be discouraged by altering the composition of the urine until it can be sterilized. Theoretically worthwhile measures include: dilution through diuresis; reduction of phosphate excretion by the administration of aluminum salts (Shorr); and increasing the solubility of calcium by the use of salicylates (Prien). I have yet to see postoperative lithiasis when all of these measures have been used, but more experience is needed to prove their value in this situation.

The advent of the modern antibiotics has permitted postoperative sterilization of the urine in most instances in which the patient returns faithfully for followup. Of particular value in infections with Bacillus proteus have been combinations of furadantin and chloromycetin with gantrisin.

It seems almost superfluous to mention violations of good surgical technique, but perhaps one should refer to such faults as: the use of sutures heavier than 0000 chromic; taking large bites of tissue with production of angulation, buckling, or spurs of pelvic wall; inadvertent placement of stitches across the lumen of pelvis or ureter, *et cetera*.

ANALYSIS OF FAILURES

Because it is a truism to say that one can learn more from his failures than from his successes, it seems worth while to discuss the former briefly, especially since the incidence is a little higher than is suggested by current reports which, however, contain few details concerning patients followed carefully for long periods. Dates indicate the year of operation for orientation in relation to the advent of antibiotics and of adjunctive methods such as the administration of aluminum salts and of salicylates. The discussion is not in chronological order.

The commonest cause of failure was postoperative nephrolithiasis due to infection with Bacillus proteus. In no instance was this organism present prior to operation. In the first case (1938), left Y plasty was successful, but the patient returned nine months later with Bacillus proteus in the urine from the right kidney, which was found to contain stones; he died after pelvionephrolithotomy. At autopsy the stricture on the operated side was corrected and there was no infection. Nevertheless, the organism was introduced via the nephrostomy.

In a second instance bilateral nephrolithiasis followed an initially successful left Y plasty in 1943. Bacillus proteus was found before discharge, but could not be eliminated. While the stones were successfully removed from the left kidney, the patient could not bring herself to submit to operation on the other side.

A third patient (1943) developed pneumonia, then thrombophlebitis post operatively, so that both splint and nephrostomy were left in situ for an inordinately long time; obstruction then recurred and intubated ureterotomy had to be done. She was then lost to followup. When she returned she had several good sized stones in her solitary hydronephrotic left kidney. These were removed and the ureteropelvic junction was adequate; the urine was sterilized with penicillin and streptomycin, and she has remained well despite several pregnancies.

Another patient (1948) had a nephrectomy elsewhere in 1950 for a calculous pyonephrosis; details cannot be secured.

A stone which did not form postoperatively played an embarrassing part in another failure (1941). A large stone, thought to be solitary, was removed from the left kidney, and Y plasty was done for a stricture. She recovered and left the state. Within a year she had pelviolithotomy elsewhere; scrutiny of our roentgenograms indicated that this stone was present at the time of the original operation, and had been mistaken for the nucleus of the one which was removed. While this has no relationship to the Y plasty, it is a failure. This, of course, emphasizes the value of roentgenography at the operating table even when one is sure that the stone is solitary.

Each of the remaining patients represents a blunder of a different sort. In the first (1936), the urine was diverted by pyelostomy with a Robinson catheter, which slipped out on the third postoperative day. It could not be reinserted, and the ensuing extravasation and infection prompted a nephrectomy which would not be considered today.

In 2 patients (1941 and 1948) recurrent strictures developed after symphysiotomy for horseshoe kidney, combined with Y plasty. A splint was used in the first but not in the second patient. The first had another plastic operation elsewhere 7 years after the first one, and now reports herself well. The second requires a semi-annual or annual ureteral dilatation to be comfortable; one wonders whether the free trip to the city does not contribute as much to her comfort as does the treatment.

In a ninth patient, already mentioned, accessory vessels left anterior to and above the junction caused persisting obstruction which was not relieved by their subsequent removal, and he had to wear a nephrostomy tube in his only kidney for the rest of his life. There must have been some element of atony of the smooth muscle of the renal pelvis.

A tenth failure (1943) was due to inadequate nephrostomy; the renal pelvis but not the ureter was duplicated. Y plasty with nephrostomy in the lower segment was followed by obstruction and infection which could not be corrected, apparently because the communication between the two segments was occluded by postoperative swelling. The bacteria were resistant to the feeble antibacterial agents then available, and the ensuing pyonephrosis required nephrectomy. A nephrostomy in each segment would have prevented this failure.

The last one (1942) cannot be explained satisfactorily because the patient refused to return for investigation, but said in the questionnaire that she "would have been better off if she had never had an operation."

COMMENT

It will be noted that three of the four failures due to postoperative lithiasis antedate the appearance of effective antibiotics and of measures designed to dissolve calculi or to alter the concentration of calcium and of phosphorus in the urine, while the fourth one (1948) preceded the advent of the few agents which are reasonably effective against Bacillus proteus. The risk of this complication now can be practically eliminated, although it can still occur if the surgeon does not take effective measures during the patient's convalescence, or if he fails to continue treatment until the urine is sterile after there are no antibiotics in the urine. Whether the techniques advocated by Hamm and Weinberg will obviate the need for such precautions remains to be seen.

Having experienced the complications due to technical errors, none of which was evident at the time of their commission, I doubt that they will be repeated. The possibility of recurrent or of postoperative strictures will always be with us, although the use of the potent antibiotics should lessen this danger as well.

The prevention of diagnostic errors is merely a matter of stopping to think before operating, and of curbing the tendency to operate while in doubt about the accuracy of the diagnosis.

Removing one stone while missing another cannot, of course, be condoned, especially since the means of prevention have been available for so long.

SUMMARY AND CONCLUSIONS

Seventy patients with seventy-three Y plasties were followed for from 5 to 24 years after operation.

Results were acceptable in 61, or 83.7 per cent, fair in one (1.3 per cent), and were failures in 11, or 15 per cent.

The commonest single cause of failure was postoperative lithiasis due to uncontrollable infection by Bacillus proteus, which should now be largely preventable.

Other causes of failure include errors in surgical technique, and mistakes in diagnosis, also preventable with a little care.

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DISCUSSION

DR. THOMAS E. GIBSON (San Francisco, Calif.): Dr. Creevy mentioned the fact that some twenty different types of plastic operations have been developed over the years. I would say there are probably nearer thirty, but when analyzed only six basic principles are involved:

1. Lateral anastomosis of pelvis and ureter (Trendelenburg 1896).
2. Resection of the ureter and re-implantation in the most dependent portion of the pelvis (Kuester 1891).
3. Heinecke-Mikulicz procedure of longitudinal incision with transverse closure (Fenger 1892).
4. Flap method with sutured pelvioureteroplasty (Foley 1937).
5. Longitudinal incision with intubation and no sutures (David M. Davis 1943).
6. Elliptical anastomosis (Nesbit 1949).

The first and oldest was Trendelenburg's, consisting of lateral anastomosis of pelvis and ureter. Of course, there have been many variations. The Trendelenburg operation is not uniformly successful because it does not produce funnelling of the pelvic outlet, and is therefore doomed to failure in a good many cases.

The second principle is resection of the ureter and reimplantation, which Kuester brought out. That was bad because cutting the ureter off squarely is bound, in a high percentage of cases, to result in a circumferential stricture at the site of anastomosis.

The next one is the Heinecke-Mikulicz procedure of longitudinal incision, which Fenger brought out in 1892. Herbst and Merricks showed years ago that it was not a good operation, the reason being that you are shortening your suture line. You are creating a kink or buckling of the ureteropelvic junction at the site of the operation.

Of the more modern methods, the first was brought out in 1937 by Foley: a sutured pelvioureteroplasty, or Y plasty, which is actually a flap method. There have been a great many changes, and I think improvements, in the original Foley flap method which are becoming more and more used today.

In 1943 Dr. David M. Davis brought out his idea of longitudinal incision of the strictured area, with intubation. This was an elaboration of his original application of the Rammstedt procedure published in 1933.

And finally there is the elliptical anastomosis of Nesbit, which has been popular, and Dr. Frank Hamm's operation using a simple vent rather than splints and drains. The elliptical anastomosis does not enlarge the caliber, but it gets away from the possibility of circumferential stricture.

I have been using the Davis operation for the last 15 or 20 years—even before Davis published his procedure—and liked it above all other operations for most of the cases of hydronephrosis that came along. To me, to do pyeloplasty without splinting or intubation was heretical. However, in the last year, since Hamm and Weinberg's bombshell, I have changed and have been trying out the various flap methods of sutured pelvioureteroplasty without drains and splints, and have been most agreeably surprised at the results.

The two operations shown in the accompanying illustrations, A and B, are to me the apotheosis of all operations for the repair of ureteropelvic obstructions.

I think the Davis idea cannot be abandoned, and it is still a very good operation if you choose to use it. In fact, in certain cases it is absolutely mandatory, and those cases, I think, are the cases where you have an elongated stricture of the ureteropelvic junction, and also in cases of severe, chronic inflammation where you have a lot of scar tissue, and inflammation either from the infection or scarring from previous operations.

A third condition, I think, where the Davis operation is mandatory is in trauma or with complete avulsion of the ureter, where suturing is out of the question.

Both operations, A and B, fulfill the postulates of Foley, which have been found essential to success: 1) absence of shortening of the suture line, 2) correction of high insertion of the ureter, 3) gradual funnelling of pelvis into ureter.

Bischoff (1953) in Germany has recommended operation A, while in England Anderson and Hynes (1949), and in this country Lich (1956) and Gardner (1956) have advocated operation B. I have merely added the vent idea of Hamm and Weinberg; the elimination of splints or intubation, and nephrostomy or pyelostomy drainage. Only a simple Penrose drain is placed down to the site of the vent.

If you are a timid surgeon and do not wish to detach the ureter from the kidney you may choose to do operation A. With either operation you arrive at the same destination. Both operations utilize the flap technique which characterized the original Foley procedure. In my experience, both operations have worked out very well, and I am very enthusiastic about them. I hope you will all try them.

Given a case which is suitable for either the Davis operation of intubated ureterotomy, or sutured pelvioureteroplasty without intubation, I would give preference to the latter procedure at the present time. A shorter, more comfortable convalescence has been the result.

There is one more thing I would like to mention before sitting down, and that is with respect to ectopic ureteral orifices. We all know they are very hard to find sometimes when they are suspected, and this little maneuver of the modified credé is useful. That is, while inspecting the vestibule, sudden pressure over the full bladder will sometimes reveal the opening, the reason being, I presume, because you usually have a sacculated or dilated ureter, and pressure over a full bladder causes that ureter to spurt forth urine.

I have a case at home now that I did that with last week, and found that urine came out of the vaginal orifice; but so far I have not been able to find the orifice of the ectopic ureter.

(Note: The ectopic orifice was subsequently found to open on the anterior wall of the vagina about 2.5 cm. above the vaginal outlet. It led to a hypoplastic left kidney, which was successfully removed.)

Dr. John L. Emmett (Rochester, Minn): Apropos of Dr. Gibson's excellent discussion of ureteral ectopia, may I briefly describe to you a rather unusual case which illustrates two interesting diagnostic points.

A girl 23 years of age stated that she had leaked urine during her entire life. Although leakage was present both day and night, it was increased when she was on her feet and when coughing, laughing or straining in any way.

When a child she had been examined by capable urologists and an excretory urogram had failed to disclose uereteral duplication. A cystoscopic examination was non-informative. Again, in her teens a similar examination had been repeated, but ureteral duplication had not been detected. Immediately before coming to the clinic a third excretory urogram had been made, with negative results, and no ureteral ectopia could be demonstrated by cystoscopy. The conclusion had been reached that the leakage was the result of urethral incompetence and the patient was referred to the clinic for plastic surgery on the urethra.

We made an excretory urogram at 8:00 o'clock one morning, which beautifully visualized a duplicated pelvis and ureter on the left side. The upper pelvis and its ureter showed the typical dilatation associated with ectopia. It seemed almost unbelievable to us that previous films made elsewhere did not show it. At 1:00 p.m. the same day cystoscopy was done, using local anesthesia, and although the urethra was carefully examined, we could not locate the ectopic orifice. We then decided to repeat the excretory urogram, using 70 per cent urokon, to see if the lower part of the ectopic ureter could be more completely outlined, to suggest the point of its termination. Much to our surprise, the duplicated upper pelvis and ureter did not visualize in any film! Two days later a third excretory urogram was made and again the duplicated upper pelvis and ectopic ureter were visualized. I have heard comments made that it is not uncommon to have such inconsistent findings in excretory urograms in cases of ureteral ectopia, but this is the first case in my experience that I can recall.

The second problem was solved in this manner: At cystoscopy constant observation of the introitus and urethral meatus revealed no leakage of urine, yet if the patient coughed or strained, about 1½ cc fluid would be ejected, apparently from the urethral meatus. This was no doubt the finding that prompted the diagnosis of urethral incontinence before the patient was sent to the clinic. Intravenous indigo carmine was given and about 20 minutes later the patient was examined. When she strained and coughed, the fluid ejected was very pale blue. We then introduced a solution of intense blue into the bladder through a catheter, and withdrew it. Still only faint blue fluid was ejected from the urethra on coughing and straining. We deduced from this that the so-called leakage came from an ectopic ureteral meatus in the urethra, which we could not visualize; that for some unexplained reason it emptied best with straining. The fact that the intense blue solution in the bladder was not ejected excluded urethral incompetence. A heminephrectomy was done, following which the patient was completely dry for the first time in her entire life.

Dr. Thomas D. Moore (Memphis, Tenn.): I should like to ask Dr. Hamm in his experimental work if he found in the late results any significant difference as to whether the mucosa of the ureter were everted or inverted in the anastomosis.

Dr. David M. Davis (Philadelphia, Pa.): The most difficult ectopic ureters to diagnose are those in which the opening of the ureter is in the mid-urethra

just inside the sphincter, because there is no urinary leakage to draw one's attention to the situation. If there is a double ureter with the other ureter entering the bladder in the usual position, and if the hydronephrotic upper pelvis becomes infected, it is often very difficult to locate the source of the trouble.

If, however, the ureter enters the urethra near the bladder, it is not so difficult to find it, but the farther down the urethra the opening is, the harder it is to locate it, particularly in the presence of heavy infection, which leads to intense congestion and edema of the urethral mucosa.

This was the situation in a case that I published over twenty-five years ago, and I was able at that time to find only four other similar cases in the literature.

I would particularly like to compliment Dr. Lich on his paper. It supplements what was done by Ostling in Stockholm as published in his magnificent monograph on hydronephrosis but it is also interesting to find that corrosion specimens of the pelves and ureters of fetuses and newborn babies were made by Albarran 50 or 60 years ago and may be seen pictured in the French *Encyclopedia of Urology*. It is very hard indeed to discover something really new.

In regard to the operations for hydronephrosis, it seems to me that the advent of the antibiotics has certainly caused, as you have all seen, a great recrudescence in the interest in true renal plastic operations and has greatly increased the percentage of success in such operations. This is probably a very good thing, since if they are successful the period of disability is greatly shortened. However, it seems to me that the same principles apply here as in all plastic operations. They must be done by people who have the ability to be meticulous and the patience to take time to be perfectionists. I am sure that many surgeons who attempt these plastic operations fail because their manipulations are too heavy-handed, their suture material too coarse and their suture bites taken too deeply.

One thing, I think, that should always be remembered is that in any kind of true plastic operation the crucial point is at the lower angle of the suture line.

Suppose we illustrate by the Trendelenburg operation. The suturing of the edges of the pelvic and ureteral incisions together, of course, creates a large orifice, but the crucial point is at the lowermost angle, at which place the suture material is put into the part of the ureter which is intact, and that is the point at which postoperative constrictions will occur, if they occur at all.

For the above reasons, it seems to me that everyone who is interested in true plastic surgery of the pelvis should emphasize in any publication most strongly the type of suture material to be used, and the depth to which the stitches should be taken.

I am delighted to see these improvements in the true plastic operations but it is still a great comfort to know that if for any reason a true plastic operation is impossible intubation and prolonged splinting can be counted on for good results.

Dr. John K. Lattimer (New York, N. Y.): I'd like to know if anybody here, including the essayists, has had any trouble from leaving the distal stump of the ectopic ureter in place?

Dr. Thomas D. Moore (Memphis, Tenn.): I have had to do a later ureterectomy following the removal of the kidney.

DR. JOHN R. HAND (Portland, Ore.): I had a patient whose ureteral stump remained infected and had to be removed later.

The interesting feature of this case was that the ureter was tremendously dilated to start with. After the upper segment was removed the caliber of the remaining portion became almost normal. Despite this, the stump remained infected.

DR. FRANK R. HAMM (Brooklyn, N. Y.): I am sorry, I didn't get your question, Dr. Moore.

DR. MOORE: I asked if in the later results in your experimental work there was any significant difference as to whether the ureter was anastomosed with the mucosa inverted or everted.

DR. HAMM: We everted in all our cases. Dr. Davelos emphasized this point, I think, but it's a well-recognized principle that has been talked about by the surgeons doing vascular surgery.

I want to give credit to Dr. Weinberg for the surgery done on the experimental animals.

DR. C. D. CREEVY (Minneapolis, Minn.): I would like to say just a couple of things.

In the first place, it isn't timidity that prompts me to leave the pelvis attached to the ureter, but rather a fine sense of discretion.

Second, I have anastomosed the one of a pair of duplicated renal pelves to the ureter of the other on one occasion in a patient with an ectopic ureter that opened into the urethra; I believe that it is worth mentioning because of the complications that preceded this operation. The little girl had complete bilateral duplication with the ureter to each upper segment emptying into the urethra. When first seen she had pyonephrosis of the right upper segment which I removed. Some months later, having observed that the ureter to the upper segment on the left was becoming dilated, I slit its orifice into the bladder, after which a very severe infection developed; and required six weeks for control, although she still had bacteriuria. At this point I anastomosed the upper pelvis to the ureter of the lower one with very satisfactory results.

I would also like to say something about intubated ureterotomy, which I do not use for ordinary purposes, because one has to leave the tube so long. I had a patient of 39 with a traumatic rupture of the ureteropelvic juncture of a solitary kidney which had gone unrecognized for 6 weeks. He had then had a nephrostomy, and subsequently an intubated ureterotomy elsewhere, the splint being left in situ for 6 weeks. When the splint was removed obstruction recurred at once and when I first saw him the patient had worn a nephrostomy for 2 years.

I wasn't going to be taken in as the first surgeon had been, when he removed the splint at 6 weeks, so I left mine in for 3 months. Again obstruction followed its withdrawal, but it was possible to pass a catheter up the ureter and pull it out through the nephrostomy. This was used to place a polyethylene splint which was left in situ for a year. Obstruction did not follow its withdrawal and the patient is well 1½ years later.

I mention this simply because there must be occasions when a very prolonged intubation—which is not ordinarily necessary—will be extremely useful.

REGULATORS OF PROSTATIC GROWTH

WILLIAM WALLACE SCOTT

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During the course of the past 10 years, this laboratory has devoted much time to an investigation of prostatic growth in the animal, in the belief that such will aid us in understanding normal and abnormal prostatic growth in man. For the most part our test animals have been the white rat and the mongrel dog. Today, I wish to summarize briefly our experiences with the rat. This can best be done with the aid of a schematic diagram (fig. 1).

Numerous observations in our laboratory have established that the total prostate weight (dorsal and ventral lobes) of the young adult white rat of the Wistar strain (250 gm.) will weigh close to 600 mg. Four to five weeks after castration, total prostate weights will average close to 60 mg. If such animals receive testosterone propionate subcutaneously in sesame oil in a dosage of 0.5 mg. every other day for 14 days, total prostate weight is restored to that of the intact controls, 600 mg.[1, 2, 3] These "reconstituted" prostate glands have been found to be identical with those of the controls in terms of water content, nitrogen content and concentration and tyrosine equivalent.

The administration of estrogenic substances to the intact animal will also result in a reduction in prostatic weight. For example, in similar rats, the subcutaneous injection of 0.5 mg. crystalline estradiol in sesame oil every other day for 14 days results in total prostate weights in the neighborhood of 150 to 200 mg. However, in our experience, in no instance has the resultant atrophy been as great as that observed after castration.

Some years ago, Huggins and his associates[4] demonstrated that the estrogen, stilbestrol, was capable of inhibiting prostatic secretion in the castrate dog, in whom a prostatic fistula was prepared, and who received daily injections of testosterone propionate. In our experience,[3] even when we administered relatively larger doses of an estrogen, almost no inhibition of prostatic growth has been observed in the castrate rat "primed" with testosterone. Specifically, the simultaneous administration of 0.5 mg. of crystalline estradiol and 0.5 mg. of testosterone propionate every other day for 14 days results in prostates which weigh

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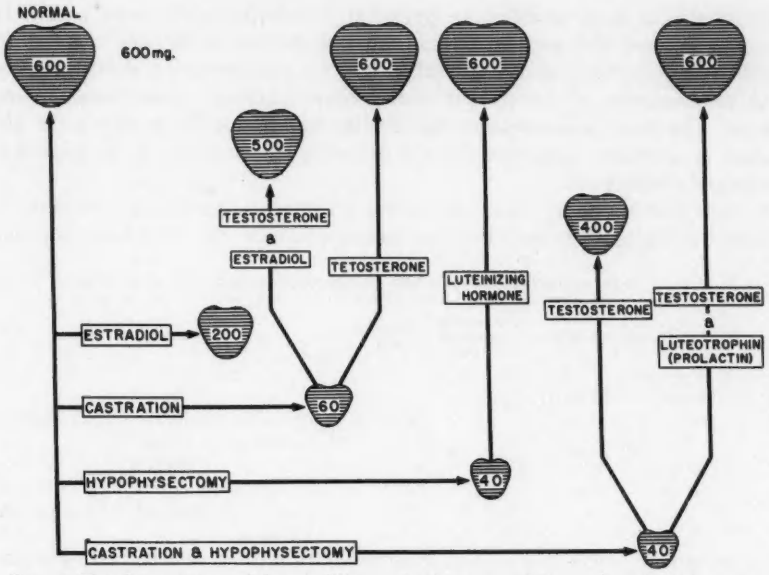


FIG. 1. Total prostate weights (milligrams) of young adult rats subjected to several endocrine manipulations.

almost as much as those of the castrate receiving the same amount of testosterone but no estradiol. If inhibition occurs in this situation, it is of the order of 15 per cent, no more. Certainly, the inhibitory effect of estrogen is not nearly so profound in the castrate rat receiving testosterone as in the rat whose testes are intact. A possible explanation for this will be presented shortly.

Removal of the pituitary gland in the rat results in prostatic atrophy which is even more profound than that observed after castration. The value of 40 mg. shown in figure 1 is not accurate, for the reason that it is extremely difficult to dissect out and accurately quantitate glands weighing less than 50 to 60 mg. However, our impression is that these glands in hypophysectomized rats are smaller than in the castrate.

Chorionic gonadotrophin, in adequate dosage, will restore the prostate weight of the hypophysectomized rat to normal. Almost surely, this occurs as the result of androgen production by the Leydig cells of the testis under stimulation by the luteining hormone.

Continuing with an explanation of the diagram, last year we reported that in rats which have been both hypophysectomized and castrated, the response of the prostate to testosterone propionate is not as great as that of the prostate of castrate rats with an intact pituitary gland.[5] This suggested that pituitary secretions have a direct or indirect hormonal influence on prostatic growth resulting from administration of androgen.

[5] Grayhack, J. T., Bunce, P. L., Kearns, J. W. and Scott, W. W.: Influence of the pituitary on prostatic response to androgen in the rat. Bull. Johns Hopkins Hosp., **96**: 154–163, 1955.

Simultaneous administration of prolactin (Squibb's luteotrophin®), ACTH, thyroxin, or chorionic gonadotrophin, and testosterone propionate was carried out in hypophysectomized castrate rats. Prolactin administration always resulted in an augmentation of the effect of testosterone propionate under these circumstances. Thyroxin adminstration has similar but less striking effects. In the absence of androgen, prolactin did not influence the prostate of the hypophysectomized castrate rat.

A priori, the inhibitory effect of estrogen on prostatic growth is not nearly so profound in the castrate rat receiving testosterone as in the rat whose testes are

TABLE 1. *Method for detecting inhibition of both* endogenous *and* exogenous *androgenic action*

Group	State of Animal	No. of Rats	Testosterone* Propionate 0.5 mg.	Compound under test	Objective
A	Intact	5 to 7	−	—	Control
B	Intact	5 to 7	−	2.0 mg.	To test any inhibition of *endogenous* androgenic action
C	Castrate	5 to 7	−	—	Control
D	Castrate	5 to 7	+	—	To establish restorative power of *standard* dose of *exogenous* androgen
E	Castrate	5 to 7	+	0.5 mg.	To test any inhibition of *exogenous* androgen
F	Castrate	5 to 7	+	1.0 mg.	To test any inhibition of *exogenous* androgen
G	Castrate	5 to 7	+	2.0 mg.	To test any inhibition of *exogenous* androgen
H	Castrate	5 to 7	+	5.0 mg.	To test any inhibition of *exogenous* androgen

* Administered every other day for 14 days (7 injections).

TABLE 2. *Inhibition of* endogenous *androgenic action by an estrogen (estradiol)*

Group	No. of Rats	Testosterone* Propionate mg.	Estradiol* mg.	Prostate weight mg.	Ratio of wts., Prostate (mg)/Body (grams)	Change of body weight grams	Testis weight grams
Intact control	5	—	—	491	1.80	−16	
Intact	5	—	0.5	168	0.61	−26	
Castrate control	5	—	—	70	0.26	−17	—
Castrate	5	—	0.5	< castrate control		−30	—
Castrate control	5	0.5	—	778	2.71	−6	—
Castrate	5	0.5	0.5	619	2.21	2	—
Castrate	5	0.5	0.25	649	2.51	−19	—
Castrate	5	0.5	0.125	703	2.38	−20	—

* Administered every other day for 14 days.

TABLE 3. *Steroids tested for possible "anti-androgenic" action*

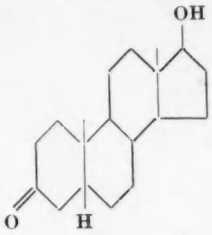
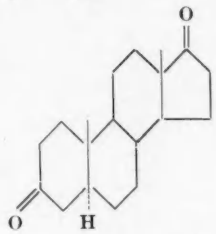
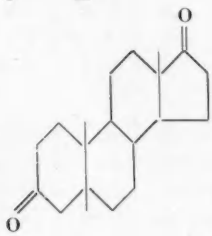
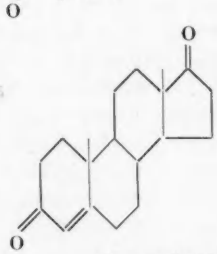
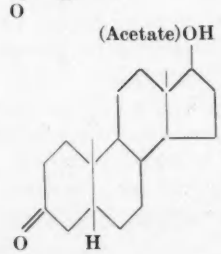
Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti-Androgenicity	
				Intact animals	Castrate animals
	Etiocholan-17β-ol-3-one	1/5	0	0	0
	Androstane-3,17-dione	1/10	0	0	0
	Etiocholan-3,17-dione	0	0	0	0
	Δ^4-Androstene-3,17-dione	0	0	0	0
	Etiocholan-17b-ol-3-one acetate	0	0	0	0

TABLE 3. (*Continued*)

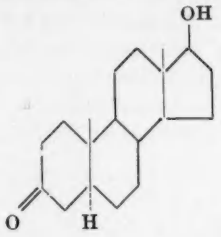
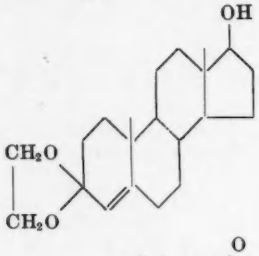
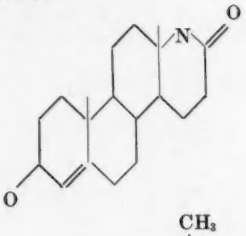
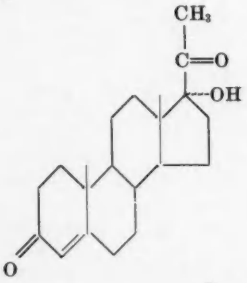
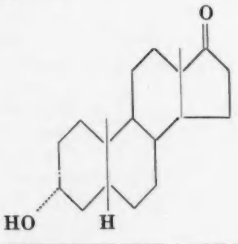
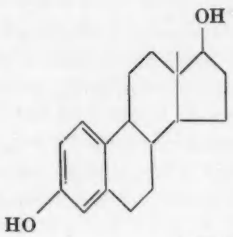
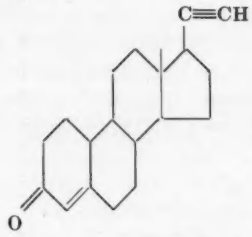
Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti-Androgenicity	
				Intact animals	Castrate animals
	Androstane-17-ol-3-one	1/7	0	0	0
	Testoketal	0	0	0	0
	Testolactam	0	0	0	0
	17α-hydroxy-progesterone	0	0	0	0
	Etiocholan-3α-ol-17-one	0	0	0	0

TABLE 3. (*Continued*)

Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti-Androgenicity	
				Intact animals	Castrate animals
	Estradiol	0	+	+	?
	19-nor-ethinyl-testosterone	?	?	+	0

intact. On the basis of our work with prolactin, it is quite possible that estrogen administration inhibits the release of prolactin by the pituitary, and as a result, prolactin is not available to potentiate the action of the *exogenous* testosterone. Whereas in the rat whose testes are intact, estrogen administration inhibits the release of not only prolactin, but the luteinizing hormone as well. Without the latter, the Leydig cells are not stimulated to produce androgen. Hence, neither *endogenous* androgen nor prolactin are available for maintenance of prostatic growth, and the result is a smaller prostate. We are unable to explain why the atrophy following estrogen administration is not as profound as after castration. On the basis of the explanation just offered for the action of estrogen in rats whose testes are intact, one would think the atrophy should be as great.

In the few minutes which remain, I would like to tell you something about our search for other chemical inhibitors of prostatic growth. This work was the subject of a report before the American Urological Association last week.[3]

Table 1 presents our method. As in the experiments described earlier, our test animal is the 250 gm. white rat, and our test object is the total weight of his prostate at the end of the experiment. The table is self-explanatory.

To test our method, we first employed a known prostatic growth inhibitor, an estrogen, in the form of estradiol. These data are shown in table 2. These results show clearly that the administration of an estrogenic steriod can alter androgenic

action, and that our method of testing permits measurement of such action. However, the mechanism by which inhibition is brought about remains to be determined, and immediately suggests the question: must a steroid have estrogenic properties—as commonly measured—to inhibit androgenic action? (The data in table 2 support a statement made earlier to the effect that estrogen inhibition of prostatic growth is not nearly as great in the castrate rat receiving testosterone as in the rat whose testes are intact.)

Satisfied that our method was capable of measuring inhibition of both *endogenous* and *exogenous* androgenic action, we proceeded to study the action of a number of steroids closely related to testosterone. Our reasons for selecting such steroids are presented in detail elsewhere.[3] The compounds tested and their chemical configuation are shown in table 3. These compounds were tested during the course of a year and one-half in 7 groups of experiments. Thus, it was necessary to use separate controls for each group. Therefore, comparisons were made within a single group *not* between groups.

TABLE 4. *Inhibition of* endogenous *androgenic action in the young adult rat by 19-nor ethinyl testosterone*

Group	No. of Rats	Testosterone* Propionate mg.	19 Nor* Ethinyl Testosterone mg.	Prostate weight mg.	Ratio of wts., Prostate (mg)/Body (grams)	Change of body weight grams	Testis weight grams
Intact control	9	—	—	534	1.59	+38	3.15
Intact	5	—	2	233	0.82	−25	2.15
Castrate control	10	—	—	32	0.10	+47	—
Castrate	5	—	2	50	0.29	−29	—
Castrate control	10	0.5	—	461	1.45	+59	—
Castrate	6	0.5	2	439	1.60	+2	—
Castrate	5	0.5	1	427	1.65	+5	—
Castrate	6	0.5	0.5	465	1.73	+9	—

* Administered every other day for 14 days.

TABLE 5. *Effects of administration of 19-nor ethinyl testosterone to immature intact rats*

Group	Body Weight, grams			Prostate, mg.			Ratio of wts., Prostate (mg.)/Body (grams)	Seminal Vesicles mg.	Testicles grams	Adrenals mg.
	Initial	Final	Change	Ventral	Dorsal	Total				
I (11) Controls, No. R_x	102	274	+172	266	162	429	1.64	501	2.66	29
II (10) * 2 mg. 19-Nor Ethinyl Testosterone	99	206	+107	25	24	49	0.24	67	0.38	34

* Every other day for six weeks.

Treated rats demonstrated: (a) infantile scrotums, (b) abdominal testes, (c) "congested" adrenals.

Referring to the first ten of the twelve steroids shown, to our knowledge, none of these had any estrogenic action. Three were weak androgens. None of the ten inhibited the prostate stimulating action of testosterone propionate in the castrate, nor caused a reduction in prostatic weight in the intact rat.

In December 1955, through the courtesy of Dr. John R. Mote, a private consultant, we obtained from Chemical Specialties, Inc., a most interesting steroid. This compound, 19-nor-ethinyl-testosterone, is shown at the bottom of table 3. As yet its properties are not clear. It is said to have progestational, estrogenic and androgenic actions, but as yet we have not subjected this compound to critical tests for such actions. We can say, that in the dosage used, it is not androgenic in the castrate rat.

As shown in table 4, this compound has a profound inhibitory effect on prostatic growth in the intact rat, indicating inhibition of *endogenous* androgen production or action, but not *exogenous*. In the immature rat, as shown in table 5, it prevents development of the testes and scrotum, testicular descent, and growth of the prostate gland and seminal vesicles. With our method of testing, it acts much like an estrogen, and a dosage of 2.0 mg. appears to be about equivalent to 0.5 mg. of estradiol.

It is effective by mouth, and at present is being tested for its effect in patients with disseminated prostatic cancer. However, it is too early to draw conclusions.

SUMMARY

A brief summary has been presented of our investigations concerning gonadal and pituitary regulation of prostatic growth in the rat.

A method has been described for detecting antagonism of both *endogenous* and *exogenous* androgenic action in the rat.

An estrogenic steriod, such as estradiol, can reduce androgenic action, especially *endogenous*, and possibly *exogenous*, but the mechanism by which this is brought about is not clear. The best explanation to us to date is that an estrogen inhibits pituitary gonadotrophins, and certain other pituitary trophic hormones, such as prolactin, which act synergistically with testicular androgen.

A new compound has been described which effectively reduces androgenic action. Whether this is a result of estrogenic properties remains to be determined.

PERINEAL SURGERY FOR CARCINOMA OF THE PROSTATE WITH FOLLOWUP DATA TO TEN YEARS

DANIEL R. HIGBEE

This group of 49 cases of operable carcinoma of the prostate was treated by perineal surgical removal between 1944 and early 1955. The group represents 22 per cent of the cases of carcinoma of the prostate treated during this period. They have been divided into two groups based on the extent of involvement at the time of the surgery as shown by the histological examination of the tissue removed.

In group 1 radical perineal surgical removal only was employed in 38 cases (table 1). In these 38 cases pathological examination of the prostate and vesicles showed the malignancy to have been confined to the prostate or to have extended somewhat into the capsule but not to the seminal vesicles. Four of these later required orchiectomy because of a local recurrence of malignancy.

In 11 cases histological examination showed the malignancy to have involved the prostate with extension to one or both vesicles, although clinically this extension had not been evident before surgery. These were treated by perineal surgical removal followed by bilateral orchiectomy as soon as the pathological extension was proved. These 11 cases comprise group 2 (table 2). These two main groups form the body of this discussion.

However, two additional groups of cases are included since both have a bearing on the problems associated with perineal biopsy. Ten cases were treated by perineal enucleation followed by orchiectomy (table 3), and 11 cases were treated by radical perineal removal in which no evidence of carcinoma was found (table 4).

The operative mortality rate for the 49 cases was 4 per cent. One death occurred on the fifth postoperative day from a large pulmonary embolus; the other death came the day of surgery from a coronary thrombosis.

The overall morbidity rate was comparatively low; however, 5 complications were pulmonary in character. All five were believed to be due to small emboli with or without accompanying evidence of pneumonia. There was one case of thrombophlebitis of one lower extremity.

Of the other actual or potential complications there were two rectal injuries which were repaired at the time of surgery, and which healed by primary union.

Some degree of lack of urinary control was present in 55 per cent of the cases immediately following surgery, and persisted for varying periods of time. One patient was still totally incontinent after 3 months at the time of his accidental death; one is slightly incontinent when he wears an abdominal belt, but is continent without it; eight were totally incontinent for from 2 to 3 months, but each eventually regained satisfactory urinary control. In 1 patient a vesical neck stricture developed due to a recurrence of malignancy and he requires an occasional urethral dilatation.

The worth of surgical removal for prostatic carcinoma either alone or in con-

junction with palliative measures such as orchiectomy, estrogen therapy or radiation therapy can be established only by followup data extending over years of time. In this group of cases, one patient with a moderate-sized local lesion, treated by radical removal only, showed no evidence of local recurrence for 7 years but eventually died of metastases. At the other extreme, one individual who had involvement of the prostate and both vesicles at the time of his surgery, which included orchiectomy, lived comfortably for 10 years and suddenly died of coronary occlusion. These are, of course, extreme illustrations. However, they point up the difficulty of attempting to draw conclusions from a relatively small group of cases.

Of the 38 cases, comprising group 1, treated only by radical perineal prostatectomy, two were operative deaths; and three are dead from causes other than

TABLE 1. *Radical perineal prostatectomy: carcinoma confined to prostate histologically, 38 cases*

Operative mortality	2	5.2%
Died of causes other than ca. 4 mos., 2½ yrs. and 3 yrs.	3	8.0%
Remaining 33 Cases		
5 years or over—17 cases:		
Recurrence of ca.:		
Dead: 5 and 8 yrs.	2	5.2%
Alive: 3–6 yrs., 1–5 yrs.	4	10.4%
Free of recurrence and alive	11	29.0%
1 to 5 years—16 cases:		
Recurrence of ca.:		
Dead: none	0	
Alive: 1–4 yrs.	1	2.6%
Free of recurrence and alive	15	39.5%

TABLE 2. *Carcinoma of prostate with extension to vesicles histologically; radical perineal with orchiectomy*

Year	Age	Active years	Length of life	Cause of death	Postmortem
1945 (DA)	69	10	10	Coronary (1 day)	No
1945 (DB)	69	8	9	Ca. of prostate	Yes
1946 (AC)	64	4	5	Ca. of colon	No
1946 (JQ)	58	4	6	Ca. of prostate	No
1949 (WC)	72	7	Alive		
1952 (LK)	63	4	Alive		
1953 (BW)	58	3	Alive		
1953 (AM)	68	3	Alive		
1953 (EB)	74	1	2	Esophageal hem.	Yes
1953 (EK)	78	3	Alive		
1954 (CF)	72	2	Alive		

TABLE 3. *Carcinoma of prostate: conservative perineal prostatectomy with orchiectomy. 10 cases*

	Length of life	Cause of death	
Died of ca. of pros.—3			
1945 (JB) 73	2½ yrs.	Recurrence—diabetes	Known ca.
1948 (JP) 73	6 yrs.	Recurrence	Unsuspected
1946 (WB) 76	2½ yrs.	Recurrence	Known ca.
Died of other causes—3			
1946 (GS) 70	5 yrs.	Broken shoulder	Unsuspected
1949 (RK) 73	5 yrs.	Cardiac decomp.	Unsuspected
1948 (RC) 63	2 mos.	Cardiac infarct	Unsuspected
Alive with ev. of recurrence—1			
1954 (A) 74	Alive 1 yr.		
Alive without ev. of recurrence—3			
1946 (CM) 66	Alive 8 yrs.		Biopsy neg.
1949 (AT) 77	Alive 7 yrs.		Unsuspected
1952 (HB) 69	Alive 4 yrs.		Biopsy pos.

TABLE 4. *Radical perineal prostatectomy: no evidence of carcinoma histologically, 11 cases*

Age	Year	Clinical	Histological diagnosis	Present status
67 (JE)	1945	Very hard gland	Hyper. + chr. pros.	Died 1951—6 yrs.
72 (R)	1949	Hard nodule	Hyper. + fibrosis	Alive 1956—6 yrs.
76 (H)	1949	Very hard gland	Hyper. + fibrosis	Alive 1953
55 (T)	1950	Hard right lobe	Hyperplasia	Alive 1956—6 yrs.
63 (McD)	1950	Hard right lobe	Hyper. + chr. pros.	Alive 1955—6 yrs.
52 (F)	1951	Hard prostate	Granuloma	Alive 1956—5 yrs.
68 (H)	1952	Hard prostate	Fibro-adenoma	Alive 1953
62 (CS)	1952	Hard nodule	Adenoma	Alive 1956—4 yrs.
73 (D)	1954	Hard prostate	Hyper. + chr. pros.	Operative mortality 9th PO day
66 (T)	1955	Hard left lobe	Chr. Pros.	Alive 1956
67 (Z)	1955	Very hard gland	Hyper. + chr. pros.	Operative mortality 6 weeks PO

prostatic malignancy (lobar pneumonia 2½ years; accidental death 4 months postoperatively; and one cardiac death after 3 years).

Of the remaining 33 cases, one is alive and free of recurrence at the end of 10 years; one is dead of recurrent carcinoma of the prostate after 8 years; two are alive and well after 7 years; six are alive 6 years after surgery (three of these showing evidence of local recurrence); five are alive after 5 years and one died of carcinoma of the prostate 5 years after surgery; five are alive after 4 years; one after 3 years; seven after 2 years; and three after 1 year. In other words, of

the 17 cases with 5–10 year followup data none died in less than 5 years' time. Two died of malignancy subsequently, four have recurrences, and 11 are alive and well. Of the 16 with 1–5 year followup data there is one local recurrence after 4 years.

In group 2, the 11 cases treated by radical perineal prostatectomy, orchiectomy and estrogen therapy, which at the time of surgery showed extension to one or both vesicles, two have died of recurrent carcinoma of the prostate in 9 and 6 years respectively, and three died of other causes (one of coronary thrombosis after 10 years, one of carcinoma of the colon after 5 years, and one of esophageal hemorrhage after 2 years). Of the remaining 6 cases, one is alive after 7 years without evidence of recurrence, one after 4 years, three after 3 years (one of these with a question of local recurrence), and one after 2 years.

Again in group 2 none have died in less than 5 years of recurrence of prostatic malignancy.

In summing up the 22 cases with 5–10 year data, none have died of a recurrence in less than 5 years. Fourteen (or 63 per cent) continue to be alive and well for longer varying periods of time.

This discussion would not be complete without the presentation of two other groups of cases. One group includes 10 cases in which enucleation and orchiectomy were accomplished. They are the ones misdiagnosed preoperatively as benign lesions, and elderly individuals with large adenomatous glands known to have some malignant involvement at the time of surgery but who, due to age or physical condition, required conservative treatment. Of these 10 cases, three died of carcinoma of the prostate 2 and 6 years after treatment, three died of other causes (one in 3 months and two 5 years after surgery), one is alive with evidence of recurrence 1 year after surgery, and three are alive without evidence of recurrence 4, 7 and 8 years respectively.

The final group of 11 cases was treated by radical perineal prostatectomy, but on histological examination the glands showed no evidence of malignancy. One of these was a prostatic granuloma with giant cell formation, two adenomatous hyperplasia, three hyperplasia with fibrosis, and five chronic prostatitis. Of this group 2 patients with chronic prostatitis died following surgery (one on the ninth postoperative day and one 6 weeks postoperatively) both of infectious pulmonary complications. Of the other nine, one died 6 years after surgery, two were lost track of after 4 years and 1 year respectively, and of the remainder three are alive and well after 6 years, one after 5 years, one after 4 years, and one after 1 year. Perineal biopsy was employed in several of the above cases.

The value of examining a frozen section of tissue at the time of surgery has fluctuated with me, since accurate diagnosis with polychrome methylene blue is difficult at best, and the surer H and E technique has not been employed until recently. Also I am not sure that biopsy *per se* does not carry some risk of spreading malignancy in the prostatic area. In 3 instances the frozen section was interpreted to be free of carcinoma only to have the report on the permanent sections run on the same tissue returned positive 5 days later. In two of these patients a radical operation was performed immediately.

In 2 cases there was no evidence of malignancy in the frozen section and none in the permanent sections, but carcinoma was found elsewhere in both glands upon removal.

Transurethral prostatic resection established the diagnosis of prostatic malignancy in 3 cases. In two of these, the diagnosis was confirmed when the glands were completely removed, and in the third there was no evidence of malignancy in the remaining glandular tissue.

As a result of these experiences, I accept the frozen section diagnosis when positive, but follow the practice of removing the prostate when an indefinite frozen section diagnosis is received, provided the clinical evidence strongly suggests the presence of malignancy. In some instances it has been advisable to obtain a perineal biopsy specimen and to defer further treatment until a report by standard staining methods is obtained.

In conclusion, the results of surgery on 49 patients with carcinoma of the prostate treated by radical perineal prostatectomy show that the outcome of this type of surgery has been comparatively favorable.

In addition, two groups of cases, one with malignancy treated conservatively and one without malignancy, but treated by radical surgery, have been reviewed. In the last group, two operative deaths in patients with severe prostatitis but without histological evidence of malignancy suggest the desirability of avoiding extensive surgery where severe chronic infection is present.

While biopsy never will be completely reliable in the detection of prostatic carcinoma, its wider use in routine perineal surgery together with yearly prostatic examinations should further minimize errors in diagnosis and increase the percentage of malignant glands found early enough to warrant complete surgical removal.

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AN EVALUATION OF ENDOCRINE CONTROL THERAPY PLUS RADICAL PERINEAL PROSTATECTOMY IN THE TREATMENT OF SELECTED CASES OF ADVANCED CARCINOMA OF THE PROSTATE FOLLOWED FIVE OR MORE YEARS

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The marked regression of primary carcinomatous lesions of the prostate that often results from endocrine control therapy has suggested to a number of observers a broadened field of usefulness for the radical perineal prostatectomy. Vallett, in 1944, seems to have been the first to use this combined therapy but, unfortunately, the patient died too soon after surgery to permit any conclusions as to its efficacy. Later in that year Parlow and then Colston suggested its use in selected cases. In December of the same year, Scott and Benjamin reported 2 cases of advanced carcinoma of the prostate without metastases, that had been treated by this method. One of these patients is alive and apparently free from tumor at this time. Colston and Brendler, in 1947, reported 1 death in 7 cases that had been followed 2 years after surgery. In 1949 Parlow and Scott presented their early results in 14 cases. The same year Gutierrez, in reporting 9 cases, expressed the opinion that the operability of advanced cases of carcinoma of the prostate would be markedly increased by this method. One year later Scott and Parlow presented a detailed report on the first 13 of 22 patients who had been treated by the combined therapy and were apparently free from tumor. Scott, in 1952, in presenting a detailed report on 21 consecutive patients treated in this manner and followed 3 or more years after therapy had been started, reported a survival rate of 85.7 per cent. The following year Sullivan and Hartwig reported that they had used this therapy in the treatment of 10 patients with advanced carcinoma of the prostate. Although the number of patients treated by this method in our clinic and followed 5 or more years is small, consisting of but 29 consecutive cases, we believe our results are sufficiently encouraging to warrant their presentation at this time.

Since an evaluation of the effectiveness of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland is necessarily influenced by the type of case included in such a study, it might be helpful if our criteria for the selection of cases were presented at this time. Obviously, those patients in whom the carcinoma, because of recent origin or latency of growth when first discovered, is so situated as to permit a reasonable chance for its complete removal by radical surgery, should not be included in this group. No patients with proven metastases, when first seen, are considered suitable candidates for the follow-up radical perineal prostatectomy, regardless of their apparently favorable response to endocrine control therapy. If the local growth has advanced enough to result in the formation of a well-defined intervesicular

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plateau or has extended for a considerable distance over one seminal vesicle when the patient is first seen, it seems reasonable to assume that invasion beyond the palpable area may have occurred even though the presence of metastases cannot be proven. In such cases, regardless of a remarkable local response, our experiences suggest that, although the follow-up radical prostatectomy may increase the patient's life expectancy and freedom from distressing urinary symptoms, it still must be considered of questionable value. However, when the cases belonging in the above categories have been excluded, there still remains a number of patients with advanced carcinoma of the prostate for whom the combined therapy may be most helpful.

These are the patients without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is first examined. It is for these patients, providing their response to endocrine therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure or, failing in this, will at least prolong the patient's life and freedom from distressing symptoms. But even some of these patients have to be excluded because advanced age or their general physical condition seems to contraindicate radical surgery.

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition. Because of their limited life expectancy and because carcinoma of the prostate often progresses very slowly in patients who are 75 or more years of age, we have not used the combined therapy in any instance in which the patient was that old when first seen. We have learned that, as a result of careful preoperative and postoperative care, proper supporting measures during operation, and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate. At least 5 of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case. As a rule, the operative risk caused by the presence of general physical debility is little, if any, greater than that of the other open operations upon the prostate for the correction of prostatic obstruction.

SUMMARY OF RESULTS AND DISCUSSION

The results of endocrine therapy plus the radical perineal prostatectomy in 29 consecutive, selected cases of advanced carcinoma of the prostate without metastases when first seen, and followed 5 or more years after treatment was started, have been most encouraging. Although in 23 of the cases the clinical impression of carcinoma was confirmed by biopsy studies made either before or very shortly after endocrine therapy had been instituted, the decision to operate was in no

way influenced by the pathological characteristics of the tissue examined. The blood studies and renal function tests were within normal limits at the time of operation. Our first patient is well and apparently free from tumor 168 months after endocrine therapy was started and 128 months after radical surgery. Among our surviving patients in this series, the shortest time that has elapsed since the institution of therapy is 70 months, and after surgery 67 months. Nine patients or 31.1 per cent died within 60 months from the time therapy was started. However, in 4 instances or 44.4 per cent of these there was no evidence of local recurrence or metastatic prostatic carcinoma at the time of death.

The cases in which death due to cancer occurred within 5 years have been reviewed in a search for the causative factors of failure. One patient, in whom carcinomatous tissue was left at operation in the region of one seminal vesicle, died of cancer 14 months after treatment was started and 7 months after surgery. This patient had definite extension over both seminal vesicles with intervesicular plateau formation before treatment was started. Another patient with carcinomatous extension from the left lobe, causing a small nodular involvement of the vesical neck when first seen, died of metastases 28 months after treatment was started and 18 months after radical prostatectomy. There was no evidence of local recurrence. A third patient with involvement of the left lobe and extension into the membranous urethra on first examination died 36 months after estrogen therapy was started and 33 months after radical prostatectomy. Perineural lymphatic involvement probably beyond the surgical field was found on the pathological examination of the tissue removed. Bilateral orchiectomy 15 months and bilateral adrenalectomy 17 months after the prostatectomy were not effective. In another patient an involvement of the left lateral lobe with extension to the membranous urethra seemed to have completely disappeared under 11 months of endocrine control therapy. However, in spite of the fact that no typical active areas of carcinoma were found on microscopic study of many sections from the surgical specimen, the patient died of a local recurrence with metastasis 34 months after surgery. The fifth patient died of cancer 58 months after treatment was started and 40 months after surgery. He had extensive involvement over the seminal vesicles when first seen, and pathological studies of the surgical specimen showed evidence of extension beyond the operative field.

In the group of patients who survived more than 5 years after operation, one died of cancer and two others are living with recurrence. The death occurred 78 months after treatment was started and 72 months after radical surgery in a patient with considerable extension over the seminal vesicles and intervesicular plateau formation, when first seen. Pathological studies of the surgical specimen indicated extension beyond the operative field. Furthermore, the patient was not placed on postoperative estrogen therapy until 42 months after surgery when the recurrence was discovered. In one patient with extension into the membranous urethra from the left lobe of the prostate, recurrence was discovered 45 months after estrogen therapy was started and 35 months after prostatectomy. He refused control therapy after his operation until the recurrence was discovered. At this time a bilateral orchiectomy was performed and he was placed back on estrogen

therapy which he has taken with marked irregularity. A transurethral resection was performed for the relief of urinary obstruction 128 months after treatment had been started. In the other living patient who was prepared on estrogen therapy, a recurrence was discovered 39 months after treatment was started and 29 months after radical surgery. Pathological studies of 15 sections from the surgical specimen revealed no typical, active area of carcinoma. He had stopped taking his estrogen therapy 12 months before the recurrence was found and refused to permit bilateral orchiectomy. It is now 86 months since treatment was started; he has no symptoms referable to his carcinoma and still does not take his estrogen with any degree of regularity. A complete autopsy was performed on another patient who died of primary carcinoma of the stomach 64 months after our treatment had been started and no evidence of local recurrence and metastatic carcinoma from the prostate could be found.

A study of our 6 patients who died of cancer and the two living with recurrence, for the purpose of explaining our failures, suggests at least two contributing factors. The first is related to the extent and location of the carcinomatous lesion when the patient is first seen. Deaths occurred in 3 instances where the growth had extended over the seminal vesicles, resulting in the presence of an intervesicular plateau. In 2 other cases there was extension from the lateral lobe into the membranous urethra and in another there was secondary involvement of the bladder in the region of the vesical neck. In a patient who died of cancer more than 5 years after the start of therapy and in two others who are living with recurrence, inadequate postoperative endocrine therapy may well have been a contributing factor. It is our firm belief that in treating cancer, especially the cases in this particular group, we should utilize as soon as possible and to the fullest extent, all the effective measures we have at our command. Where the patient will consent he should be prepared for surgery by estrogen therapy plus bilateral orchiectomy and after operation he should be maintained on estrogen therapy for several years.

Fortunately, there is now available sufficient reliable data to permit a very satisfactory evaluation of the relative effectiveness of the various types of therapy used in treatment of patients with advanced as well as supposedly confined carcinoma of the prostate, who were without metastases when first seen. As a control series we have the report by Nesbit and Plumb on the survival rate at 6 month intervals on 273 cases that were treated by the methods in use before the introduction of endocrine therapy and followed for 60 months after their first visit. Using the case material supplied by the members of the Urosurgical Society, Nesbit and Baum, in 1950, reported the survival rate at 6 month intervals for 60 months on a series of 324 cases of advanced carcinoma of the prostate without metastasis, that were treated by the various types of endocrine therapy that are in common use today. To the above we have added our series of 29 consecutive, selected cases of advanced carcinoma of the prostate without metastasis when first seen, that were treated by endocrine therapy plus the radical perineal prostatectomy, and also a series reported by Jewett of 78 cases of carcinoma of the prostate without metastasis, in which there was no evidence

of extraprostatic extension prior to the time of the radical perineal prostatectomy. In the latter series endocrine therapy was not used.

One cannot examine the results of the various types of therapy presented in table 1 without being deeply impressed by the progress that has been made in the treatment of cancer of the prostate gland during the past two decades. Whereas the survival rate for 60 months was but 10 per cent in the control group it was 29 per cent in the diethylstilbestrol series, 31.2 per cent in the castration cases, 43.6 per cent where estrogen and castration were combined and 68.9 per cent in the group treated by endocrine therapy plus the radical perineal prostatectomy. It would seem that, inasmuch as extension beyond the confines of the prostate was present to some degree in all our cases when first seen and whereas there was no apparent extraprostatic involvement in the group reported by Jewett, the 68.9 per cent 5-year survival rate in the former compares very favorably with the 51.3 per cent in the latter. The higher 5-year survival rate in our series might be explained in part, at least, by the fact that in every case a favorable response to endocrine therapy had been demonstrated. Although it is perhaps unwise to attach too much significance to the results of a comparative study in which one group is considerably smaller than the others, it is interesting to note that the percentage of deaths not attributable to cancer, in this group, was greater than that of any of the others.

In the treatment of selected cases of advanced carcinoma of the prostate without metastases when first seen, endocrine therapy and the radical follow-up perineal prostatectomy seem to complement each other very nicely. Sometimes in the cases where the extraprostatic extension is too marked to permit complete

TABLE 1. *Type of therapy and percentage survival at 6 month intervals in series of cases of carcinoma of the prostate without metastases at time of first visit*

Type of therapy	Number of cases	% Survival at six month intervals										% deaths not from prostatic cancer
		6	12	18	24	30	36	42	48	54	60	
Control (Nesbit and Plumb)	273	72.0	54.0	39.0	32.0	25.0	22.0	—	14	—	10	—
Diethylstilbestrol (Nesbit and Baum)	63	93.7	88.9	82.6	76.2	63.5	55.6	43.0	33.5	31.0	29	32
Castration (Nesbit and Baum)	183	90.8	83.7	72.0	65.1	61.3	51.4	45.0	37.7	35.0	31.2	22
Diethylstilbestrol and castration (Nesbit and Baum)	78	93.6	84.7	80.8	74.4	71.8	65.4	57.8	53.9	53.9	43.6	30
Endocrine therapy plus radical perineal prostatectomy (Scott)	29	100.0	100.0	96.5	96.5	93.1	89.6	79.3	79.3	72.4	68.9	44.4
Radical perineal prostatectomy, no endocrine therapy (Jewett)	78	(without preoperative evidence of extraprostatic extension) (recurrence in 24 cases)									51.3	36.4
Total	704											

extirpation when the patient is first seen, the initial response to endocrine therapy is such as to make this procedure possible at a future date. Furthermore, it would seem that the damaging effect of endocrine therapy upon the cancer cells within the prostatic capsule might tend to decrease the possibility of local and distant spread at the time of surgery. Postoperative endocrine therapy is necessary to destroy, or failing in this, to stem the growth and spread of any small foci of cancer that may have been left at surgery. We believe that, even where there is no evidence of extraprostatic extension when the patient is first seen, he should be maintained on a postoperative course of estrogen therapy for at least 4 years after the radical perineal prostatectomy. Finally, the follow-up radical perineal prostatectomy removes the source from which local extension may recur and metastases spread, once the effectiveness of the hormone control therapy has been lost.

We think that our results are sufficiently encouraging to warrant further trial of this therapy. Even if in our remaining cases the carcinoma is not so satisfactorily controlled, we believe that this treatment in most instances, when judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease. As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction. Furthermore, Vest's introduction of the traction-suture method of anastomosing the vesical neck and the membranous urethra has done much to prevent the incontinence that has occasionally resulted from this type of surgery.

CONCLUSIONS

The results obtained by endocrine therapy plus a follow-up radical perineal prostatectomy in the treatment of 29 consecutive selected cases of advanced carcinoma of the prostate without metastasis when first seen have been presented.

The survival rate of 68.9 per cent for 5 years is apparently better than has been obtained in the treatment of similar cases by any of the other methods in common use today.

Although this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results warrant a further trial of this therapy.

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TREATMENT OF CANCER OF PROSTATE BY INTERSTITIAL INJECTION OF Au 198: STUDIES IN PROBLEM OF DISTRIBUTION

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Since March 21, 1951, 389 patients with inoperable cancer of the prostate but without distant metastasis have had as their sole treatment, or as part of their treatment, the interstitial injection of the radioactive isotope of gold, Au 198. Our experiences with this therapy have been previously reported.[1, 2, 3] We have emphasized the careful selection of patients—patients in good general condition with group 1 lesions which were definitely operable have been reserved for radical prostatectomy while those with evidences of distant spread, group 3, have been treated by conservative, palliative therapy. Those with group 1 cancer who would not submit to radical operation or whose general condition made it unwise and those with locally inoperable lesions in good general condition and with no evidences of dissemination beyond the regional lymph nodes were chosen for this treatment. It was emphasized also that the method showed promise, but that the problem most pressing for solution was that of adequate distribution of the radioactive material throughout the neoplasm.

The objective of this therapy was not only to destroy the local lesion which could be eradicated by local excision as proven by the good results obtained in the stage 1 group by radical prostatectomy, but also to destroy neoplasm in the surrounding fascias, in the regional lymphatic channels and in regional lymph nodes. It has been variously demonstrated that 1–1.5 mc of Au 198 per cc of tissue will achieve a cancerocidal response so that it would seem that if this could be achieved satisfactorily in the prostate, in the surrounding tissues and in the lymphatic channels and nodes without serious complications, our mission would be accomplished.

It is the purpose of this report to discuss the problems of adequately distributing the radioactive material as outlined above upon the basis of clinical studies on the 389 patients thus far treated, and other experimental studies.

DISTRIBUTION WITHIN THE PRIMARY CANCER ITSELF

In the vast majority of 389 cases the weight of the local lesion was under 80 gm. so that a total dose of 80 mc well distributed within the prostatic tumor would be quite satisfactory if the material remained localized long enough. It

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was found that satisfactory distribution of the major portion of the dose administered was very difficult to obtain at one sitting, but that attention to certain factors seemed to be of definite help. These may be discussed under the headings of: the addition of a spreading factor; the utilization of the fascial planes about the prostate; the volume of injection; the technique of injection; and multiple injections.

Experiments in mice utilizing hyaluronidase as an additive to the solution to be injected have shown that this enhances distribution (fig. 1). *In vitro* experiments in prostatic tissue seem to indicate that pretreatment of tissue with hyaluronidase would enhance distribution still further but this has not been done in patients. The question has been raised as to whether the use of a spreading factor causes the material to leave the site of injection sooner than is desirable.

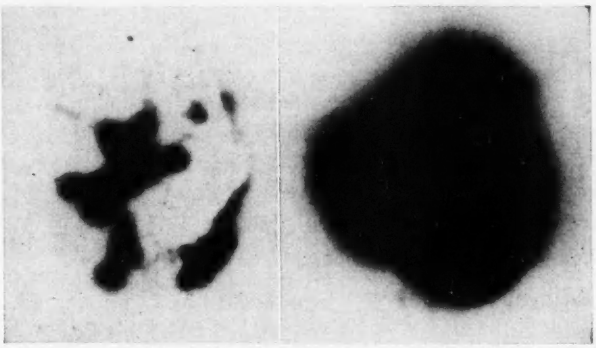

FIG. 1. Radioautographs illustrating improvement in distribution of solution in mammary tumors of mice using hyaluronidase solution as diluent instead of saline. Left shows autograph with saline. Right shows autograph with use of hyaluronidase. Note improvement.

FIG. 2. Roentgenogram of prostatic region immediately after injection of 4 cc 50 per cent diodrast solution into prostatic region. Note that capacity of prostatic capsule has been exceeded and material has entered venous system.

There is no clinical evidence to support this proposition. On the contrary, there is clinical and experimental evidence to indicate that rapid entrance of the Au 198 into the bloodstream is associated with the use of an excessively large volume of diluent (fig. 2).

The relatively small size of the average prostatic tumor and the anatomy of

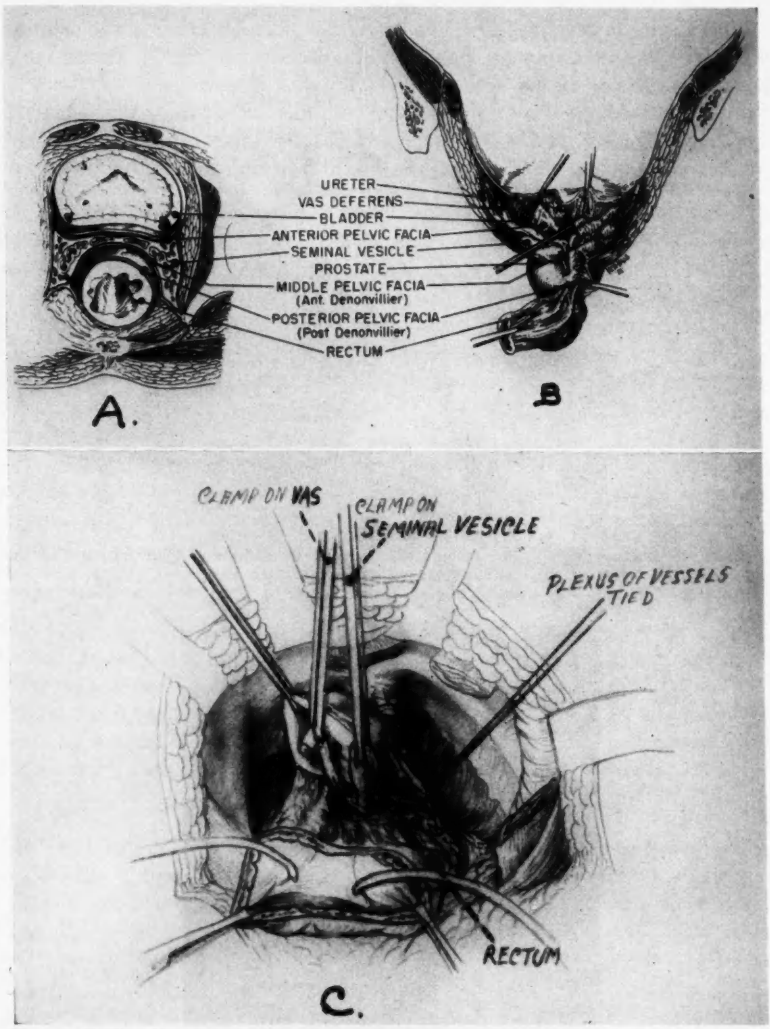

FIG. 3. Studies of anatomy of fascial compartments about prostate and seminal vesicles. Note relationship to rectum. In *C*, drawing made during radical retropubic prostatectomy, note relationship of seminal vesicles and vascular pedicles to rectum. Note that these are two separate fascial compartments.

the fascial planes within and about the prostate and nearby structures should be utilized when injections are made (figs. 3 and 4). Studies on postmortem specimens and in actual patients with the injection of India ink show that these fascial septa and planes direct the course of the injected material in such a way that it collects around the prostate just inside the capsule. If this is punctured or broken through, the material may collect around the rectum. The large compartments containing the seminal vesicles and the lymphatics and vessels of the prostate partially encircle the rectum in their course to the lateral pelvic wall (fig. 3) and if broken through or if too much radioactivity is placed in them, rectal damage is to be feared. This was the cause of the high incidence of rectal ulceration in the first 50 cases of our series. The role of septa within the prostate and the method of distribution along these and along fascial planes outside the prostate are illustrated well by radioautographs of tissue obtained at various times after injection.

One of the most important observations to be made from the clinical and experimental studies with regard to the distribution is the influence of volume upon the distribution. The average prostate plus its carcinoma will not be able to tolerate more than 2 to 3 cc of total volume. If more than this is injected the material gets outside the fascial compartments and is directed upwards by the fascia of Denonvilliers—upward and laterally into the compartments about the seminal vesicles and along the fascial planes towards the lateral pelvic wall. The plane of distribution is around the rectum laterally and when a great quantity is injected, it is these areas which are most markedly irradiated; and in the original cases in which rectal ulceration developed, it occurred at those points. If we are to obtain, therefore, our goal of approximately 1 millicurie of radioactive gold per 1½ gm. tissue and at the same time keep most of this radioactivity in the area to be injected, a very small volume of material must be injected. It would seem preferable to have a solution whose original concentration is 25 to 30 millicuries per cubic centimeter so that it would be possible

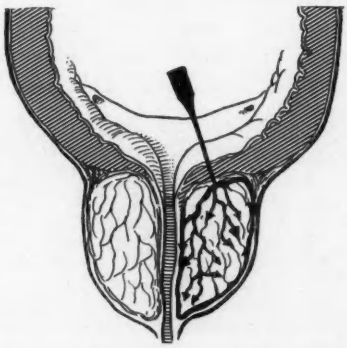

FIG. 4. Diagram illustrating course of injection fluid if small volume is injected at vesical neck. Material flows through adjacent septa to capsule which then directs it around prostate and cephalad. If too great a volume is used, solution simply flows on through septa and then upward away from prostate.

TABLE 1. *Complications*

	1–100	101–187	Total
Rectal irritation	22	0	22
Rectal ulceration	8	0	8
Rectal stricture	8	0	8
Colostomy	5	0	5
Calculus formations	6	8	14
Rectal-urethral fistula	1	0	1
Leukopenia	2	0	2
Exfoliative dermatitis	1	0	1
Urticarial rash	1	0	1
Delayed wound healing	1	0	1
Total complications	55	8	63
Total cases	33	8	41

in an 80-gm. prostate, for instance, to use only 3 or 4 cc of solution and at the same time, be injecting approximately 100 millicuries of radioactivity.

In our first 80 or so cases, the volume that was used was too high. Approximately 20 to 50 cc of diluent was used so that approximately ¾ of the radioactivity which was injected did not stay in the prostate but moved along the fascial planes outside the prostate around the rectum and on upward along the pelvic areolar tissues. Of course, some of this was picked up by the regional lymph nodes which was desirable but the dosage delivered to the original tumor was much less than was calculated and the dosage delivered to the fascial planes about the rectum was infinitely higher, in many instances 50 to 60 per cent of the total dosage. It is for this reason that the high percentage of rectal difficulties occurred. Once the total volume was cut down, rectal ulceration disappeared as a complication (table 1).

Figures 5 and 6 show the effects of increasing volume upon the distribution within the prostate. In these instances needles were inserted perineally and 50 per cent urokon solution was injected and x-ray films exposed. Figure 5, *B* shows the picture obtained with the injection of 2 cc of material. Figure 5, *C* shows 5 cc of material. Notice the quite extensive distribution throughout the prostate fol-

FIG. 5. Effects of increasing volume upon distribution within prostate. *A*, needle inserted into right lateral lobe. Before injection. *B*, Injection of 2 cc of 70 per cent urokon into right lateral lobe. Note distribution being directed by septa and fascial planes across midline and within prostatic tissue. *c*, Same case. Needle has been inserted into left lateral lobe and 5 cc urokon solution injected. Note spread outside of prostate and into venous system.

FIG. 6. Effects of increasing volume upon distribution within prostate. *A*, needle inserted perineally using long Lowsley tractor to help guide it into place. *B*, 1 cc 70 per cent urokon solution injected. Note that solution remained within prostate. *C*, 2 cc solution injected. Left side of prostate is filled to overflowing. More volume would have led to extravasation outside prostate and probable venous entrance.

lowing the intraprostatic septa with only 2 cc of material. When the larger amount is used, notice breakthrough and spread into the fascial planes and into the veins. This latter spread of the radiogold solution into the veins about the prostate and from these into the larger veins is very noticeable upon injection of large volumes of material and probably is the cause of the 7 to 15 per cent practically immediate appearance of the radioactive material in the bloodstream when more than 2 to 3 cc volume is used (fig. 7). These are not related to the use of hyaluronidase and are not due to the rapid absorption of the material but are

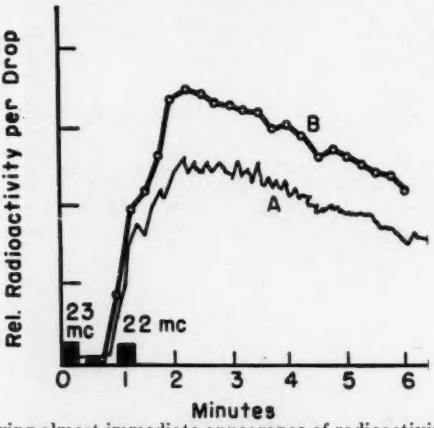

FIG. 7. Chart showing almost immediate appearance of radioactivity in arterial blood of right arm following perineal injection of too large a volume of material. (From work of Rounds in our laboratory.)

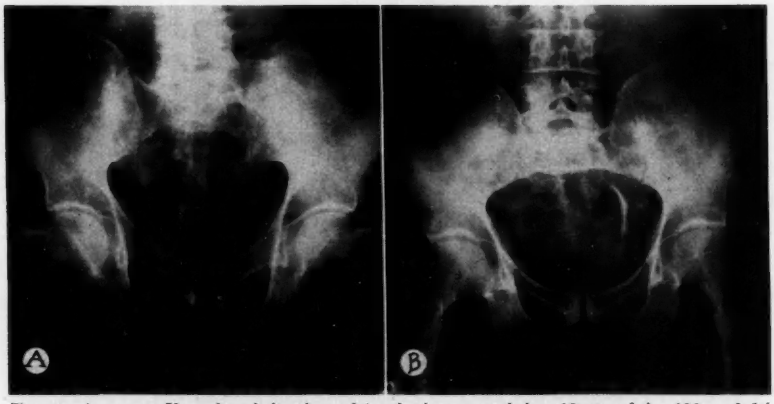

FIG. 8. *A*, x-ray film after injection of 1 solution containing 10 mc of Au 198 and ½ cc 70 per cent urokon. Note good localization in residual carcinomatous nodule on right side. *B*, poor distribution of radioactive gold following perineal injection as demonstrated by 70 per cent urokon. Secondary injection will be necessary. No influence upon tumor nodule in left lateral lobe of prostate is to be expected. In fact, since material was injected into and around bladder wall, bladder irritation may be expected here.

rather due to the direct vascular entrance of the material by breaking into the veins in the prostate when large quantities of material are injected under moderate pressure. It would seem from these studies that the use of pressure, when large quantities of material are used, is to be deprecated.

If there is much scarring and a small volume is used there is little likelihood of marked spread of the injected solution (fig. 8, *A*).

The technique of injection plays an important part in the obtaining of correct distribution. Each fascial compartment should be entered and a small amount of the solution injected into it. If the volume is too great the compartment will be broken open and leakage away from the desired area will occur. If the wall of a compartment is punctured (fig. 8, *B*) material will go to an undesired area and an undesirable result be obtained. The best approach is the combined transvesical and extraprostatic (fig. 9), but at times this is not possible and in such instances

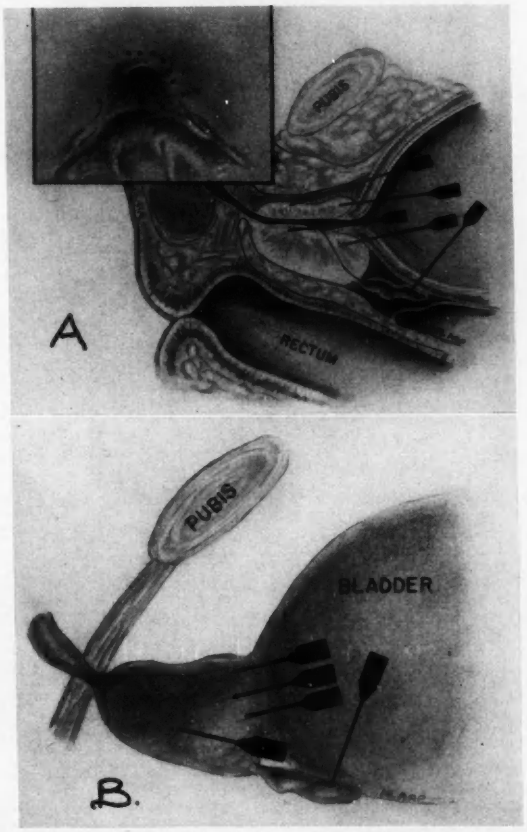

FIG. 9. Diagrams illustrating combined transvesical, extraprostatic approach to injection of radioactive material.

the closed perineal, open perineal, and transrectal routes may be used. The fundamental principle is the laying down of multiple small volumes of the radioactive material throughout each compartment. An example of such a good distribution is illustrated in figure 10.

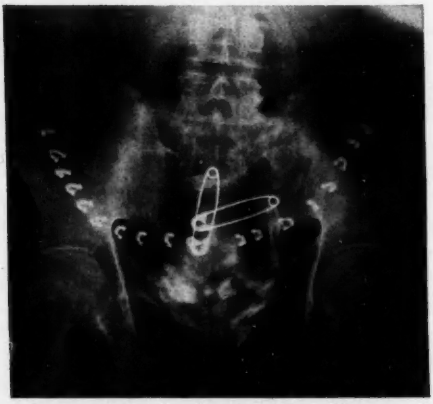

FIG. 10. X-ray film taken immediately after operation. Note excellent distribution after combined transvesical and extraprostatic technique of injection.

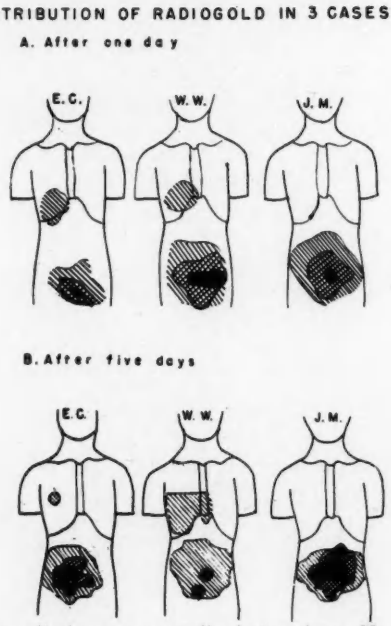

FIG. 11. Post-injection radiation survey studies in 3 patients. Note that 5 days after injection radioactivity is still localized in pelvic region.

The question is sometimes asked, "How long does the material, after it is properly placed, stay in place? Does it stay in place long enough to produce the desired effect?" Post-injection radiation survey studies, in addition to clinical results, show that it does (fig. 11).

In spite of the use of a correct volume, a correct dose, a correct distribution throughout the gland as far as the urokon x-ray film shows, some areas of carci-

TABLE 2. *Route of administration*

	1–100	101–187	Total
Primary			
Retropubic-transvesical	89	60	149
Perineal	10	27	37
Transrectal	1	0	1
Secondary			
Retropubic-transvesical	1	2	3
Perineal	31	38	69
Transurethral resection	1	0	1
Number receiving:			
1 Secondary injection	15	17	32
2 secondary injections	12	7	19
3 secondary injections	4	12	16
4 secondary injections	1	0	1
5 secondary injections	0	1	1

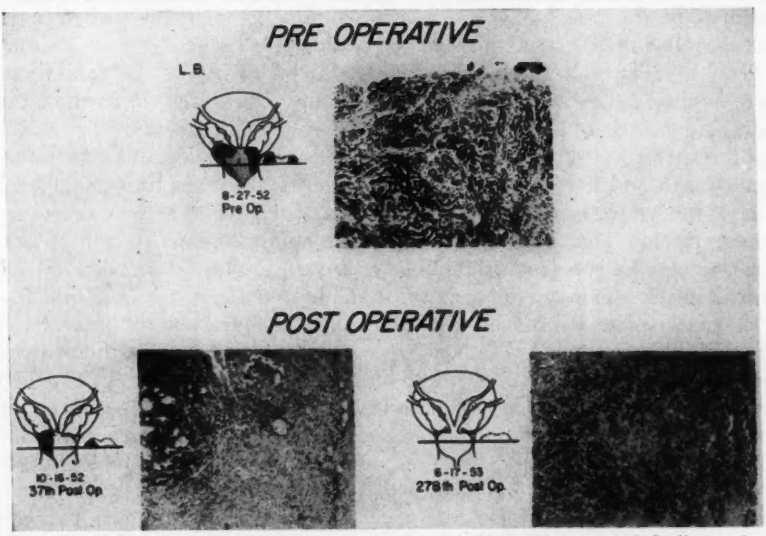

FIG. 12. L. B., 57-year-old white man admitted 8-27-52. Note rectal findings after 2 months of estrogen therapy. Received 125 mc. injected by combined transvesical, extraprostatic route. Note rectal findings 2 months later (10-16-52). Secondary injection at this time resulted in rectal findings as illustrated on 6-17-53. Two biopsies taken 1 year and 1 year, 6 months later by perineal punch and transurethral methods have been negative. Prostate rectally has remained unchanged.

noma may not be destroyed. In this instance secondary injections are safe and are of great value. Table 2 shows their incidence in our series; figure 12 illustrates their use in a patient followed by an excellent result.

DISTRIBUTION TO ADJACENT FASCIAS AND ADJACENT LYMPH CHANNELS AND NODES

If the fascial compartments of the prostate and the seminal vesicles are not overfilled, little radiation, except from the gamma emission, will get to the areas about the prostate. It is wise, therefore, to soak these areas with 10 to 15 mc. or more on each side. If gross masses of tumor are present, these should be infiltrated with the Au 198 just like the prostatic tissue was. Even if the thin fascia does not hold the gold, it will get irradiated from the material which sticks to its surface and quite adequate irradiation obtained if the neoplasm present is not too thick. If grossly involved nodes are present these must be removed surgically since adequate distribution throughout the node is difficult to obtain when large masses of tumor are present. One of the striking facts observed in this group of 389 patients with local prostatic carcinoma was an incidence of 30 per cent grossly involved regional lymph nodes. In many of these instances the local lesion was quite small. The Au 198 distribution to uninvolved or very slightly involved regional lymph nodes from a well injected cancerous prostate, which was small enough to completely remove, is illustrated by the case in figures 13 and 14.

Figure 13 illustrates the radioautograph of a prostate removed by retropubic radical prostatectomy following the injection 1 week previously of material in the apex of the prostate about an area of carcinoma which was considered operable. It will be noted that the radioautograph shows sufficient counts to indicate a cancerocidal dose in a goodly area of the apex of the prostate and there is also, in the regional iliac nodes, a cancerocidal dose in some of these nodes. None of these nodes were involved by carcinoma. These studies indicate that properly injected material can produce a cancerocidal dose in a satisfactorily injected area and that a cancerocidal dose can be delivered to regional lymph nodes if the lymphatics to these are not blocked. Figure 15 depicts microscopic sections through areas which show a positive radioautograph. It will be noted that the material spreads fairly diffusely through the fascial connective tissue, giving multiple points of radioactivity. It will be noted in figure 15, *B* that when carcinoma involves the areolar tissue and fatty tissue about the prostate, the spread of the material is not through the cords of cancer but through the areolar tissue carrying the nutritive vessels to and from the carcinoma.

Recognizing the fact that the problem of distribution is an extremely important and difficult one, we have followed the course in many instances where large masses of carcinoma are present, obviously making the problem of distribution more difficult, of removing as much as possible of these masses. Usually what is done is a radical prostatectomy, retropubically, with instillation of small amounts of the radioactive material into the surrounding pelvic fascia and into the prostatic pedicles. At the same time, involved regional lymph nodes are removed. We have followed this course in 10 instances and have found that aside from a somewhat more febrile convalescence, the postoperative course was

FIG. 13. Distribution of radioactive gold in prostatic region 1 week after the injection of mc. of radioactive gold into a hard area in the apex of the prostate which was an operable prostatic cancer. *1*, Diagram showing removed prostate and adnexa and location of radioactivity. *2*, Gross radioautograph of right lateral lobe. *3*, Gross radioautograph of left lateral lobe.

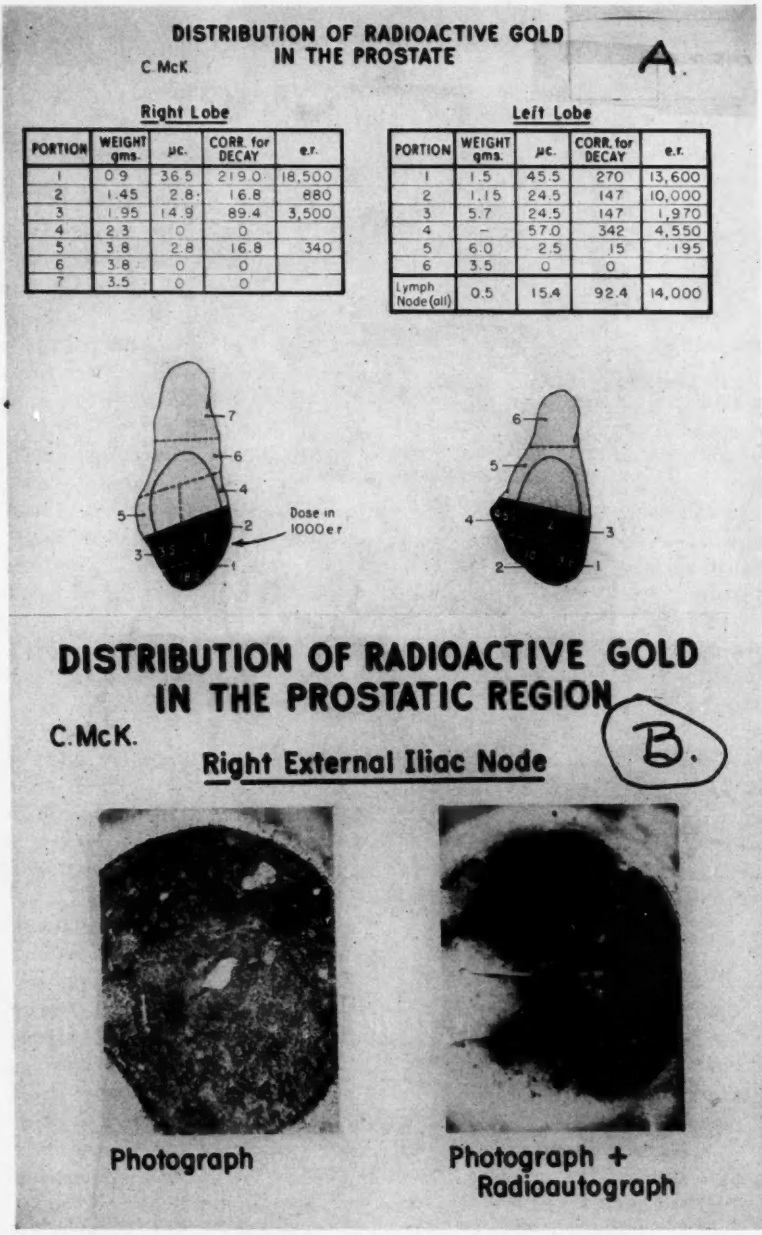
DISTRIBUTION OF RADIOACTIVE GOLD
IN THE PROSTATE
C. McK.
A.
Right Lobe
PORTION | WEIGHT gms. | μc. | CORR. for DECAY | e.r.
1 | 0.9 | 36.5 | 219.0 | 18,500
2 | 1.45 | 2.8 | 16.8 | 880
3 | 1.95 | 14.9 | 89.4 | 3,500
4 | 2.3 | 0 | 0 |
5 | 3.8 | 2.8 | 16.8 | 340
6 | 3.8 | 0 | 0 |
7 | 3.5 | 0 | 0 |
Left Lobe
PORTION | WEIGHT gms. | μc. | CORR. for DECAY | e.r.
1 | 1.5 | 45.5 | 270 | 13,600
2 | 1.15 | 24.5 | 147 | 10,000
3 | 5.7 | 24.5 | 147 | 1,970
4 | – | 57.0 | 342 | 4,550
5 | 6.0 | 2.5 | 15 | 195
6 | 3.5 | 0 | 0 |
Lymph Node (all) | 0.5 | 15.4 | 92.4 | 14,000
Dose in 1000 e r
DISTRIBUTION OF RADIOACTIVE GOLD
IN THE PROSTATIC REGION
C. McK.
B.
Right External Iliac Node
Photograph
Photograph +
Radioautograph

FIG. 14. Distribution of radioactive gold in prostatic region 1 week after injection of 30 mc. of radioactive gold into a hard area in the apex of the prostate which was considered an operable prostatic cancer. Same case as figure 13. *A*, note that lobes have been divided off into sections and estimated roentgens of energy delivered to these sections are shown in charts. Note that "probable" cancerocidal dose has been delivered to section 1 of right lateral lobe and sections 1, 2, and 4 of left lateral lobe. Note, in lower line of chart under left lobe, that dose to right iliac node removed was "probably" also cancerocidal. *B*, photograph and radioautograph of the lymph node removed. Note marked concentration of radioactivity in outer portion of node. No nodes in this patient were grossly involved with cancer. This node was removed simply for study with regard to its radioactivity.

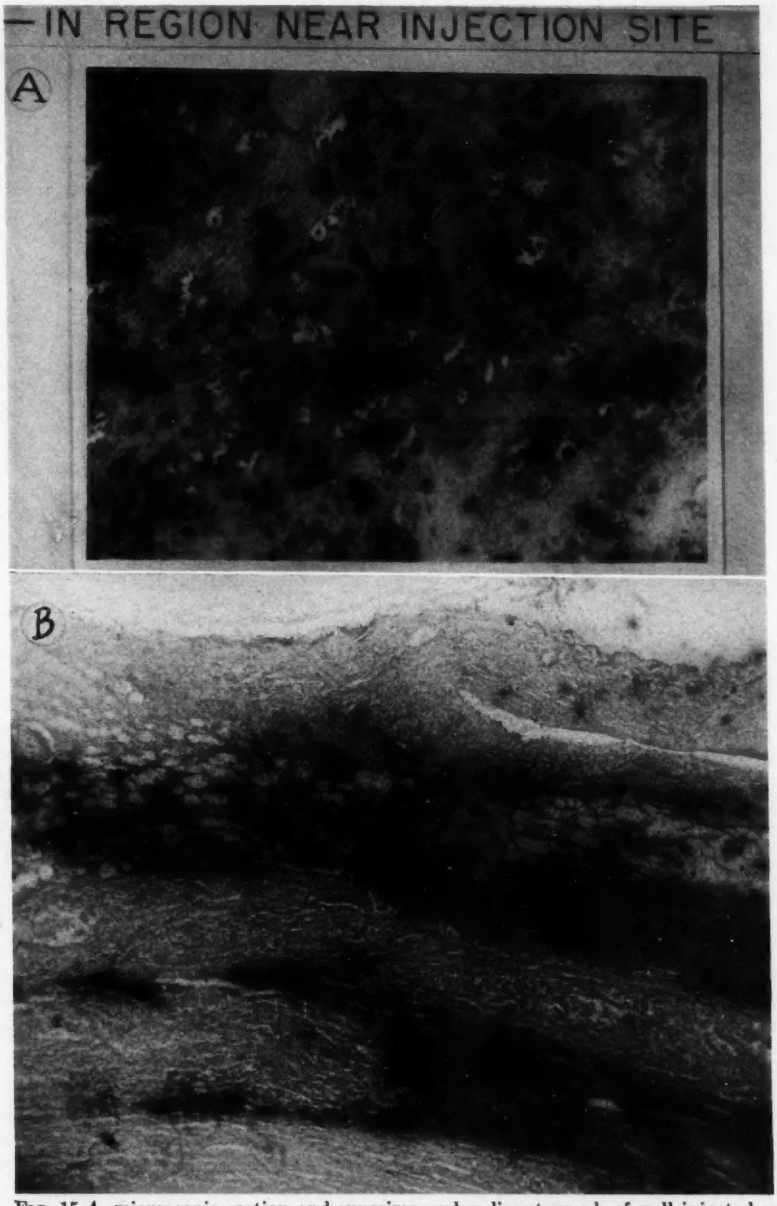

FIG. 15 *A*, microscopic section and superimposed radioautograph of well injected area of prostatic cancer 1 week after injection.

B, radioautograph superimposed upon microscopic section of tissue outside prostatic capsule markedly invaded by neoplasm. Note that radioactive material travels in areolar tissue around growing cords of neoplastic tissue.

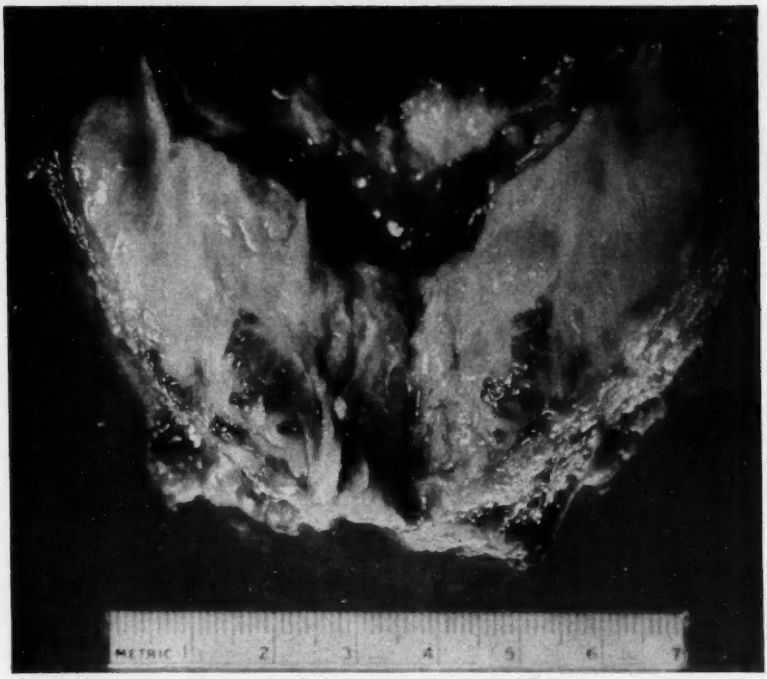

FIG. 16. Prostate of J. G., 66-year-old white man, who had transurethral resection on July 7, 1954, for carcinoma of prostate with retention. On July 22, 1954, retropubic exposure of prostate was carried out. No enlarged regional lymph nodes were found. Prostate was seat of large cancer involving both lateral lobes, anterior lobe, subtrigonal area and both seminal vesicles. There was induration lateral from prostate on each side. By sharp dissection, prostate and as much of seminal vesicles, subtrigonal area, and prostatic pedicles were removed. Pedicles and adjacent areas on each side were infiltrated with a total of 50 mc radioactive gold in 3 cc diluent. Postoperative course was uneventful. Patient as of March 1956 was well with nothing palpable rectally which might indicate neoplasm, and voiding well. No endocrine therapy of any kind was being used. Of course, it is still too early to know about ultimate result but result 20 months after therapy is satisfactory.

essentially unchanged, there was no evidence of damage to the rectum in any case and the results were quite good. In some instances apparent cures were obtained. In others, although healing of the wound, etc. took place, carcinoma recurred with the requirement of further palliative therapy. A good example of such therapy is indicated in figure 16.

In conclusion, studies of the problems connected with the distribution of the radioactive material through the cancerous prostate have shown that satisfactory distribution can be obtained in many instances. Some of the factors which seem to be of help in obtaining such distribution are: 1) the use of hyaluronidase as a spreading factor; 2) the use of very small volumes of material to carry the required radioactive dose; 3) proper utilization of fascial septa and fascial planes;

4) the utilization of technique for studying distribution after injection, such as the use of urokon or diodrast as a diluent, and postoperative radiation surveys; 5) multiple injections at 2 month intervals; and 6) the removal of masses of tissue and grossly involved lymph nodes to reduce the amount of tissue which needs to be irradiated, thus cutting down on the danger of obtaining inadequate distribution and on the need of using very large total and therefore relatively dangerous doses of radioactive material.

FURTHER EXPERIENCES IN TREATMENT OF CARCINOMA OF PROSTATE WITH RADIOACTIVE CHROMIC PHOSPHATE AND YTTRIUM CHLORIDE

GEORGE J. BULKLEY, VINCENT J. O'CONOR AND JOHN A. D. COOPER*

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The treatment of prostatic carcinoma by means of interstitial irradiation with radioactive gold (Au 198), chromic phosphate (P_{32}) and yttrium chloride (Yt 90) has been carried out by several groups over the past three years. Our experiences with these substances have recently been brought up to date and published.[1] The results have been somewhat less than originally hoped for, but are sufficiently encouraging in some cases to make us believe that the method has some value in the control of this usually fatal disease. Further experiences following the use of radioactive yttrium chloride and chromic phosphate have prompted this report.

The selection of patients and method of injection have been described elsewhere.[1] The additional patients reported here were all injected by means of multiple needles introduced through the perineum, guided by a finger in the rectum. We have continued to utilize this method because we feel that distribution is equal to that obtained by the retropubic route and that we are better able to protect the rectum while placing the needles. In addition, the perineal procedure carries little morbidity and the hospital stay is usually quite brief.

The series of patients receiving radioactive yttrium chloride now totals 12 and the results are summarized in table 1.

It is evident from table 1 that only 2 patients out of the total group of 12 have received any clinical benefit from the yttrium injection. Seven of this group have had post-injection perineal biopsy performed and six of these biopsies showed active adenocarcinoma. One patient was injected 3 times and biopsy material obtained 3 months following each injection remained positive. Two patients were injected twice and both had positive biopsies after the second injection. None of this group of patients had received either estrogens or orchiectomy, although those showing progression of disease in spite of interstitial irradiation have recently been placed on estrogen therapy. One patient of this group has had three negative needle biopsies at 3-month intervals and continues to do well.

Dosages of radio-yttrium have ranged from 19.5 mc. to 40 mc., depending on the size of the tumor. There were no complications noted in any of these patients.

Experimentally, we felt that radioactive yttrium offered promise in the

This work was made possible in part by funds from the Urological Research Fund of Chicago Wesley Memorial Hospital.

* Markle Scholar in Medical Science.

[1] Bulkley, G. J., Cooper, J. A. D. and O'Conor, V. J.: Treatment of carcinoma of the prostate with radioactive material. J. Urol., **75**: 837–845, 1956.

TABLE 1. *Yttrium (Yt 90), 12 patients*

	Cases
Died of disease	2
Living with no change rectally	8
Living with gland softer and smaller	2

TABLE 2. *Chromic phosphate (P 32), 5 patients*

	Cases
Died of disease and bone marrow depression	2
Living without clinical improvement	3

control of prostatic carcinoma, chiefly because of its high energy beta rays and rapid fixation to tissue. Clinically, this does not seem to be the case. Urinary loss and loss into the bloodstream have been equal to that experienced with gold and chromic phosphate, so that the dose remaining in the prostate is probably quite a small percentage of the total injected dose. Although this series of patients is too small to be statistically significant, it seems to indicate that radio-yttrium has no advantage over radio-gold in our experience. Since radioactive gold has the added possibility of greater penetration due to the gamma ray component and is so much easier to produce and obtain commercially, it seems doubtful that radioactive yttrium will be widely used.

The series of patients with prostatic carcinoma receiving radioactive chromic phosphate is summarized in table 2.

None of the patients who received chromic phosphate apparently benefited from the injection. There have been rather alarming complications in four patients of this group, apparently due to radiation damage to bone marrow. These case reports are presented below in detail.

CASE REPORTS

Case 1. See figure 1. A.E. was admitted to the hospital on March 17, 1955 with complaints of urinary difficulty. Past history revealed a previous transurethral prostatic resection at another hospital in 1954. No pathological diagnosis of this tissue could be obtained. Examination on entry revealed a hard, nodular, fixed prostate which proved to be adenocarcinoma on perineal needle biopsy. Initial laboratory studies: hemoglobin 12.9 gm.; white blood cell count 5,700, with normal differential; blood urea nitrogen 7.9 mg. per cent; and acid phosphatase, 0.28 Bodansky units. X-rays showed no signs of bony metastases.

On April 4, 1955, perineal injection of 21.5 mc. radioactive chromic phosphate was accomplished with four No. 22 gauge needles introduced perineally, and the Flocks' syringe. The hemoglobin was 11.9 gm. and white blood cell count 4,800 a week after injection.

The patient was re-admitted August 15, 1955 for followup biopsy which was done on August 17, 1955 and was positive for active adenocarcinoma. Laboratory studies: hemoglobin 12.6 gm.; hematocrit, 37 per cent, white blood cell count 4,300, with normal differential; blood urea nitrogen, 14.1 mg. per cent; and

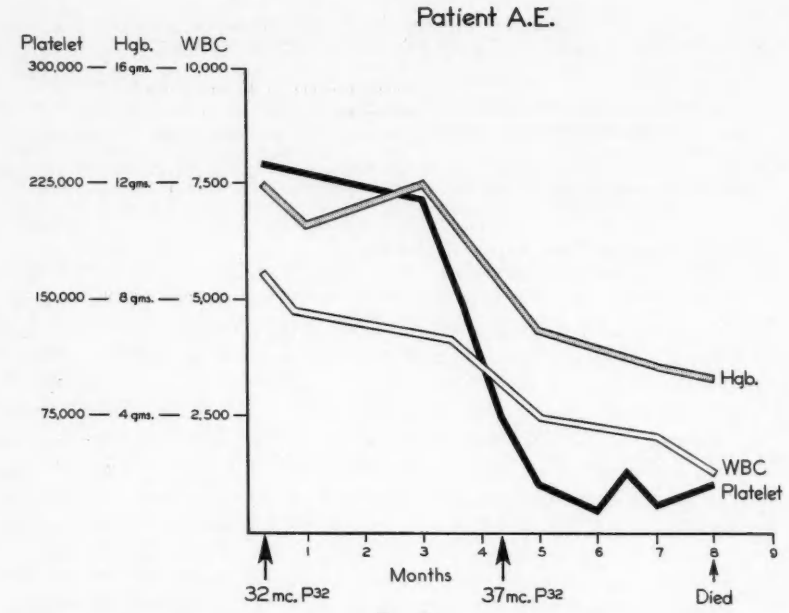

FIG. 1

acid phosphate, 0.2 Bodansky units. On August 24, 1955, 38 mc. of radioactive chromic phosphate were injected perineally using 4 needles and the same technique as previously described.

The patient was re-admitted on September 29, 1955 complaining of shortness of breath, swelling of the abdomen and severe epistaxis. Examination revealed a hard, flat prostate and a liver enlarged to three fingerbreadths beneath the costal margin. Admission white blood cell count was 2,500, hemoglobin 7 gm., hematocrit 27 per cent, bleeding time, 1 minute; coagulation time, 9 minutes; prothrombin time, 100 per cent; blood urea nitrogen, 15.4 mg. per cent; acid phosphatase, 0.03 units; platelet count 16,000. Bone marrow aspiration revealed hypoplastic marrow with depression of all elements and no sign of metastatic carcinoma. The platelet count rose to 104,000 under treatment and fell to 32,000. The blood urea nitrogen rose steadily over a 3-month period to 38 mg. per cent and the acid phosphatase to 19.2 units. The white blood cell count rose to 5,000 under treatment and later fell again. A second perineal biopsy on November 30, 1955 showed adenocarcinoma. The patient became progressively worse and died on December 28, 1955. Autopsy showed that death was due to a combination of pancytopenia from depression of bone marrow, arteriosclerotic heart disease and carcinoma of the prostate with some bony metastases which were not thought to be extensive enough in themselves to cause death. The pathologist felt that bone marrow depression, probably from radiation damage, significantly contributed to the fatal outcome.

Case 2. J.K. was admitted on January 10, 1955 with a complaint of difficulty

in voiding and was found to have large residual urine. Rectally, the prostate was enlarged, hard, nodular and fixed. Perineal biopsy showed adenocarcinoma of the prostate. Laboratory studies: hemoglobin 13.7 gm.; white blood cell count 6,100; hematocrit, 46 per cent; acid phosphatase, 0.64 Bodansky units; blood urea nitrogen, 24.5 mg. per cent. On January 17, 1955, 28.6 mc. of radioactive chromic phosphate were injected perineally using five No. 22 gauge needles and the Flocks' syringe. On February 14, 1955, a transurethral prostatic resection was done; sections of tissue removed showed adenocarcinoma with some areas of necrosis and inflammatory reaction from the radioactive material.

The patient was re-admitted on May 19, 1955 and rectal examination showed little change from the previous findings. Laboratory studies were not significantly changed except that the white blood cell count was 4,500. Perineal biopsy showed active adenocarcinoma and 75 mc. of radioactive gold was injected perineally.

He was re-admitted on December 1, 1955 for eye surgery. A second perineal biopsy showed active adenocarcinoma. Bone marrow puncture showed no tumor cells and no pathologic diagnosis was made. We have no evidence that there was any significant radiation damage to the bone marrow in this patient. There was very little change in the prostatic carcinoma rectally after two injections of radioactive material.

Case 3. W.S. had had a diagnosis of carcinoma of the prostate made in 1951 following a transurethral resection of the prostate. He was placed on estrogens by mouth for 3 years and in 1954 a bilateral orchiectomy was done. On admission to the hospital on June 2, 1955 he complained of back pain. Rectal examination showed an enlarged, hard, nodular prostate gland. Laboratory studies: white blood cell count 6,200, normal differential; acid phosphatase, 0.3 Bodansky units; hematocrit 45 per cent; blood urea nitrogen 9.3 mg. per cent. X-ray of the pelvis showed metastatic lesions. Perineal needle biopsy was negative but, because of the previous diagnosis and findings of metastatic carcinoma, a perineal injection of 39 mc. of radioactive chromic phosphate through five No. 22 gauge needles was accomplished.

The patient was admitted to the Veterans Hospital at Wood, Wisconsin on November 26, 1955 and died on November 29, 1955. On admission, he showed generalized icterus, multiple widespread petechiae and ecchymoses. There was a thrombocytopenia and afibrinogenemia noted, although exact figures are not available. Bone marrow studies showed metastatic carcinoma and generalized atrophy. Autopsy showed extensive metastatic carcinoma of the prostate and the cause of death was recorded as this plus the changes in the bone marrow and peripheral blood. Sections of the liver showed fatty degeneration and congestion with extramedullary hematopoiesis. The pathologist stated that the thrombocytopenia and icterus were hard to explain on the basis of findings. It is our impression that these changes may have been due to radiation damage.

Case 4. See figure 2. W.B. was admitted to the hospital on June 16, 1955 for control of diabetes and the nephrotic syndrome. On physical examination, a nodule was palpated in the prostate and a perineal biopsy of this nodule on July 8, 1955 was positive for adenocarcinoma of the prostate. On July 25, 1955

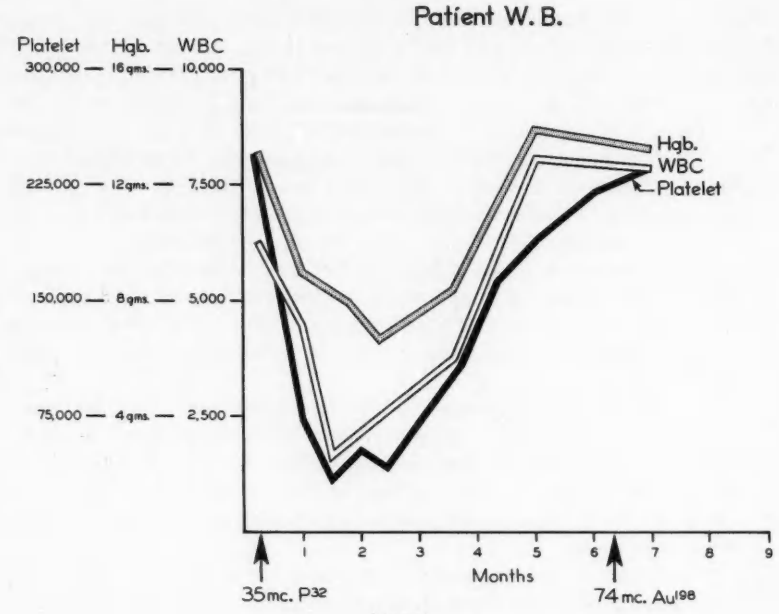

FIG. 2

perineal injection of 35 mc. of radioactive chromic phosphate was carried out using the technique described above.

The patient went home and returned on August 6, 1955 for massive gastric hemorrhage. An emergency gastric resection was done by the surgical service; however, the patient continued to bleed from the gastrointestinal tract for ten days following surgery. Laboratory studies showed the platelet count to vary from a low of 28,000 to 164,000 and the white blood cell count to vary from a low of 2,000 to 4,800. He had multiple petechiae following surgery. No bone marrow studies were done. Recovery took place in several weeks.

The patient was re-admitted on December 4, 1955 and laboratory studies revealed: white blood cell count 8,700 with normal differential; hemoglobin 15.3 gm.; hematocrit 44 per cent; platelets, 288,000; bleeding and coagulation times, normal; blood urea nitrogen, 12.4 mg. per cent; and acid phosphatase 0.94 Bodansky units. Needle biopsy of the liver showed fatty degeneration. Needle biopsy of the kidney showed arteriolar nephrosclerosis. Repeat biopsy of the prostate on December 14, 1955 showed adenocarcinoma of the prostate. An injection of 74 mc. of radioactive gold was done through five No. 22 gauge needles introduced perineally.

Followup examination on March 22, 1956 showed no softening of the gland on rectal examination. No further complications ensued.

It is probable that the severe gastric hemorrhage and changes in the blood

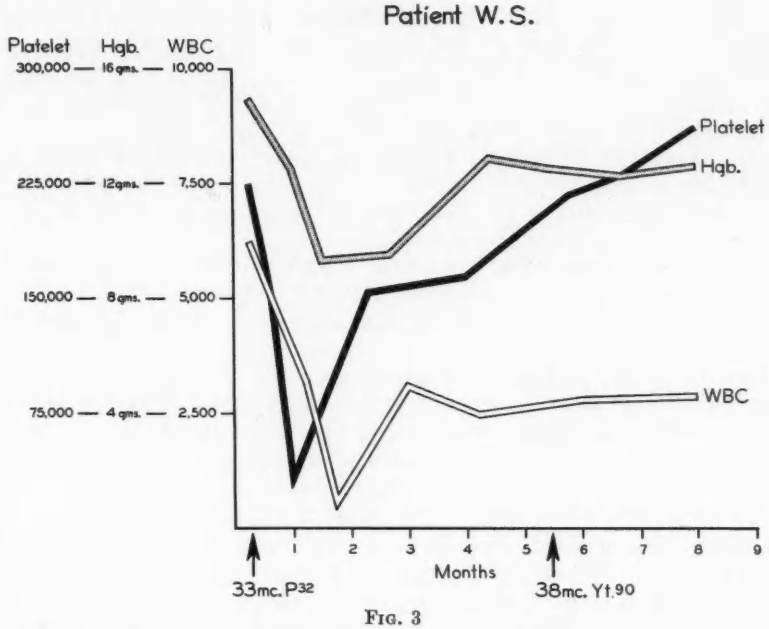

FIG. 3

were due to bone marrow depression from radioactive chromic phosphate. At the time, we were not alert to such complications, or we would have avoided the gastric resection which was probably unnecessary.

Case 5. See figure 3. W.S. was admitted on July 22, 1955 complaining of low back pain and pain in the right hip. Rectally, the prostate felt typical of carcinoma with extension outside the capsule. X-rays showed no evidence of metastatic lesions. Laboratory studies: Hemoglobin, 16.5 gm., hematocrit, 50 per cent; white blood cell count, 6,500; normal differential; blood urea nitrogen, 15.7 mg. per cent; acid phosphatase, 0.57 Bodansky units. Perineal biopsy showed adenocarcinoma of the prostate.

The prostatic mass was injected with 33 mc. of radioactive chromic phosphate using the usual technique. No immediate complications ensued.

The patient was re-admitted on September 7, 1955 for severe epistaxis, purpura and ecchymoses of the arms, legs, mouth and trunk. In addition, he had hematuria and was passing blood clots in the urine. The liver was palpable, smooth and not tender. The white blood cell count was 3,500 on admission and fell to 550 12 days later, and finally rose to 3,000 a month later. The platelet count was 24,000 on admission and rose to 54,000 ten days later and finally to 180,000. The hemoglobin was 14.6 gm. on admission and fell to 10.1 gm. and later rose to 14.1 gm. Bone marrow aspiration on September 12, 1955 showed markedly hypocellular marrow with depression of all elements. Repeat aspira-

tion on October 28, 1955 showed an essentially normal marrow. The patient made a good clinical recovery and it was believed that his pancytopenia was due to radiation effect on the bone marrow.

The patient was re-admitted on January 4, 1956 and laboratory studies showed: white blood cell count 2,900, normal differential, hemoglobin 15.3 gm.; blood urea nitrogen, 15 mg. per cent; platelets, 164,000; bleeding and coagulation times normal. X-ray showed no metastases. Repeat Silverman needle biopsy of the prostate showed active adenocarcinoma. On January 17, 1956, 38 mc. of radioactive yttrium were injected perineally.

Followup visit on March 8, 1956 showed a platelet count of 220,000, hematocrit of 34 per cent and normal bleeding and coagulation times.

Followup visit on April 12, 1956 revealed a hard, fixed, nodular prostate. The patient was free of symptoms.

Review of these cases seems to indicate that sufficient radiation damage to bone marrow with resultant pancytopenia occurred in four of the five patients receiving radioactive chromic phosphate. In case 1, this was apparently directly related to the fatal outcome. In case 3, the pancytopenia and fatal episode were probably due in part to radiation damage to the liver and bone marrow and in part to metastatic carcinomatosis. Case 4 had a severe bleeding episode which was nearly fatal and from which he made an ultimate recovery, as did case 5. There seems to be little doubt that these latter 2 cases suffered from considerable radiation damage to hematopoietic organs. Previous studies have shown that immediately following intraprostatic injection of radioactive chromic phosphate as much as 28 per cent of the total injected dose may be recovered from the circulating blood, and, certainly, some of this may become fixed in the bone marrow with resultant damage.[1] The possibility also exists that some free phosphorus may be present in the colloidal suspension, and this, of course, would have a particular affinity for bone marrow.

A recent report by Prout et al. who reported hemorrhagic diathesis in metastatic prostatic carcinoma due to the production of a proteolytic enzyme produced by the carcinoma may account for some of the bleeding tendencies observed.[2] Previous reports of Huggins and Vail,[3] Tagnon et al.[4] and others all indicate that metastatic carcinoma of the prostate may produce a fibrinolysin leading to afibrinogenemia. The role that these factors may play in the above cases is difficult to assess, but several of these patients did not have extensive metastatic disease, and, therefore, we feel that the blood changes were due chiefly to radiation change. We have discontinued the use of radioactive chromic phosphate because of the above findings, and because we have failed to achieve any significant control of the carcinoma with this substance.

[2] Prout, G. R., Siegel, M., Cliffton, E. E. and Whitmore, W. F.: Hemorrhagic diathesis in patients with carcinoma of prostate. J. A. M. A., **160:** 840–846, 1956.

[3] Huggins, C. and Vail, V. C.: Plasma coagulation and fibrinogenolysis by prostatic fluid and trypsin. Am. J. Physiol., **139:** 129, 1943.

[4] Tagnon, H. J., Whitmore, W. F., Schulman, P. and Kravitz, S. C.: The significance of fibrinolysis occurring in patients with metastatic cancer of the prostate. Cancer, **6:** 63, 1953.

SUMMARY

Further experiences following the use of radioactive yttrium chloride seem to indicate that it has no advantage over radioactive gold in the treatment of patients with carcinoma of the prostate.

Severe radiation damage to the bone marrow following the intraprostatic injection of radioactive chromic phosphate is reported and has led us to discontinue the use of this substance.

Five patients failed to benefit clinically from the intraprostatic injection of radioactive chromic phosphate.

720 N. Michigan Ave., Chicago 11, Ill.

DISCUSSION

DR. J. A. C. COLSTON (Baltimore, Md.): I should like to discuss Dr. Winfield Scott's presentation.

Ten years ago, at the meeting of this society I presented a short series, only 7 cases, which on clinical examination were too far advanced; they did not fulfill the criteria we like to follow for cases for radical operation. That is, the tumor on rectal palpation had extended obviously beyond the prostate or into the seminal vesicles, but no metastases were present.

The response of these patients to estrogen therapy was most gratifying, and in this particular small series some cases that were unsuitable for radical operation regressed to such a degree that this operation was carried out successfully from a technical point of view in the seven cases.

Now, please remember that all these 7 cases were inoperable when first seen clinically. Also, they followed one criterion that I think is most important; and that is, these patients must be in the younger age group and must have good life expectancy, so that unless the conditions are unusual—of course, it's impossible to lay down a didactic rule, but we usually think quite a bit before we operate on anybody over 70, and I think Dr. Scott feels the same way.

Those of you who were in Boston and heard Dr. Elmer Belt's presentation* certainly noticed that 75 of his patients were over 70 and most of the deaths he had were in that group of 75 who were over 70.

I think by following these criteria rigidly one can certainly reduce the mortality, and we are fortunate enough to have a series of about 100 in whom there has been no operative death.

Now, as it was 10 years ago when I presented this small series, I think I'd like to tell you what has happened to them. Remember, please, that they were all inoperable clinically when first seen.

One died in 6 years without recurrence or metastasis on autopsy. Another one died in 6 years with some blood dyscrasia. Again autopsy showed no metastasis. All four of the others died with recurrence and/or metastasis.

Now, one is alive—let's see—13 years after the operation, and if you will bear with me for just a second I'd like to show you two slides which show, I think, the disappointments, and then the pleasant surprise that one will occasionally get.

(Slide) This patient was seen by Dr. Hugh Young in 1945, and it is obvious that it is a questionable case for radical operation, but after 3 months of estrogen therapy he returned. He was subjected to radical operation in 1945, and he died about three or four months afterwards with extensive recurrence and metastases. This was a case that we thought—I hate to use the word "cure" because I'm never sure there was ever a cure—but this was a case that we thought would have an excellent prognosis.

(Slide) Now here was a general surgeon who came in also in 1945, and he had

* J. Urol., January, 1957.

this picture on rectal examination—obviously inoperable—and after about six weeks of estrogen therapy the condition has regressed to this point (indicating), where we felt that his future would be better if we carried out a radical operation, as far as comfort and longevity, but the prognosis for a complete eradication of the disease was indeed bad.

I'm glad to say this patient is now alive and well 13 years after operation, and has been practicing surgery until just recently, when he retired.

I think, therefore, that Dr. Scott has given us a very excellent contribution, and has stimulated us in attempts to make these inoperable patients operable.

With patients whom I think are suitable for radical operation we have been giving estrogen therapy for at least a short time, in the hope that some malignant cells might become necrotic, and that the chances of recurrence or metastasis would be less.

Dr. John K. Ormond (Pontiac, Mich.): About a year ago I was talking with a urologist who has done a great many perineal radical operations, and he expressed great skepticism as to whether he had ever completely eliminated cancer from those patients. It stimulated me to look up my own cases, of which there were 35, a small series compared to some of the series here.

There were one or two points which surprised me, which I have not seen discussed much in other cases. One was the retention of sexual powers. Out of the 35, four, we knew, retained their sexual powers. Some of the others may have. We never asked. One of those was 61 years old, but the most interesting thing and possibly the most important thing is that the only two in this group who were under 50 retained their sexual powers.

Another point in this group was apparently that if local recurrence did not take place in the first three years, the patient could be considered a cure. That I have to qualify by telling of two patients who disappeared from observation after two years and returned three years later with recurrence.

Then, another interesting point that has come up, not in connection with this case but in connection with other cases that I have discussed with other men: Dr. Bohne of the Henry Ford Hospital told me recently of a man on whom he had done a perineal biopsy who was impotent afterwards. I can't help believing that it must have been psychic.

Dr. William Wallace Scott (Baltimore, Md.): I really have nothing of importance to add, except to say that I have tried this new compound, 19-norethinyl-testosterone, in one patient with disseminated prostatic cancer. This man had received no hormonal therapy previously. Following administration of this new compound for 2 weeks, his serum acid phosphatase fell from 9.9 (Bodansky units) to 1.9. He felt better and experienced a mild euphoria, equivalent in my experience to that observed following 50 mg. of cortisone daily.

This compound is being made available for clinical trial, and I have suggested to Dr. John Mote that it be made available to several of you here today. Perhaps you will hear from him soon.

Dr. Winfield W. Scott (Rochester, N. Y.): Due to the limited presentation time I was unable to refer to the early and very interesting work on this subject

by Drs. Colston and Brendler. Because we felt that the occasional patient in his seventies with better than average physical and mental findings was entitled to any benefits the combined therapy might offer, we arbitrarily decided against its use in any individual who was 80 or more years old when the lesion was first discovered. As a matter of fact, since only 4 of our patients were more than 70 years of age when first seen we have approximated the age limit adopted by Dr. Colston. In our series only one of four patients with extension over the seminal vesicles and intervesicular plateau formation is well and apparently free from cancer.

I believe that Dr. Ormond's observation regarding the maintenance of satisfactory erectile power, in the occasional case, following the radical perineal prostatectomy has been observed and noted by others. A patient of ours, 57 years of age, was able to resume and fulfill his marital sexual obligations in a normal manner until his death in an aeroplane accident 30 months after surgery.

Dr. Rubin H. Flocks (Iowa City, Iowa): I'm going to add, with regard to volume that we use now, that we try to use as small a volume as possible, and try never to exceed 6 cc dividing it up into multiple small punctures of very small amounts. Perineally, where there isn't a good chance for the thing to spread up along the fascial planes, we never use more than about 2½ cc in divided doses, so that the dose as far as volume is concerned is very much smaller than it was; and I believe, for example, that if you use much more than that you are bound to get some of it into the bladder, and therefore into the urine, and some of it into the fascial planes.

(Slide) Now, here's a slide showing the complications in the first 187 patients of our series, after about two and a half years. You can see the difference. All of these rectal complications occurred in the first 50 cases. The most important complication that we have had since then has been sloughing off prostatic tissue, which produced stone formation in the prostatic urethra and bladder, and which could usually be dealt with quite satisfactorily by transurethral means.

Also leukopenia, which was in one case quite similar to the several that Dr. Bulkley and Dr. O'Conor reported with chromic phosphate, occurred in the first 50 patients, and we have not seen any leukopenia of any severity at all since that time. There have been some patients, however—a very small number, about six or seven—who have had some drop in their white count following perineal injection, which is probably on the basis of the direct entrance of some of the material into the bloodstream.

With regard to the late results, we have at the present time in the first 100 patients 38 alive with a four-year or more followup. Of those 38, about half of them—and I don't have the exact figures—seem to be perfectly all right clinically. On the other hand, others have metastasis and are on hormonal therapy at the present time.

Dr. Vincent J. O'Conor (Chicago, Ill.): I want to emphasize the fact that what we showed here today, the small groups of the three types that Dr. Bulkley presented, were patients upon whom all other therapy had been withheld. Now, it's very difficult in a private practice or even in a ward practice such as we have at Chicago Wesley Memorial Hospital to withhold all therapy from a patient with

carcinoma of the prostate except with a new modality like this. In fact, I'm not sure that I'm sufficiently hard-boiled to do that. But Dr. Bulkley got permission to withhold all therapy on this group of patients, all other therapy except injection of radioactive material.

Of course, as far as I'm concerned—and I have stated this a good many times, and I think especially before this group—to me there's only one real approach to the solution of the treatment of carcinoma of the prostate, and that's the approach that Dr. Scott is making in his experimental work. I don't think that we know really a great deal about the pathogenesis of carcinoma of the prostate. It's a very, very imponderable disease.

In the old days, before we had estrogens, I have followed individuals with carcinoma of the prostate for as long as 18 years with large, infiltrating growths, and these men had no treatment whatsoever, and their carcinoma was proven at autopsy at the end of 18 years.

I had another man who lived 14 years. The man who lived 18 years lived the last 5 years of his life with a suprapubic tube in place.

So, I think there are many grades of activity of carcinoma of the prostate. There is the occult, inactive type, and the intermediate type, and I think there are these types that are stimulated whether it's endocrine or not and become very malignant and metastasize and cause rapid death.

Now, Dr. Flocks says that he's now injecting small amounts of material into the prostate. Well, I can't see the rationale of that at all. In the first place, our number one problem and our only excuse for using radioactive isotopes in the prostate is to try to get enough of the material in there and to have it diffuse sufficiently to destroy the active cellular carcinomatous tissue.

We have nothing like this series of gold cases. We have treated something like 50 or 60 patients. We have about 60 patients in whom we have injected radioactive gold, and despite the fact that a lot of this material went into the blood stream we have never had a serious systemic complication; so I don't think it makes any difference whether he gets it in the bloodstream or not. It surely does with chromic phosphate, but I don't think it does with gold, and I think Dr. Flocks is defeating his own suggestion when he starts cutting down on the amount of radioactive material that he is injecting into the prostate. I don't think his results are going to be nearly so good with his next group of patients, if he keeps this work up, as he has reported in the past.

He admits that he has gotten rid of his rectal complications. We have never had them. We have had a couple of retropubic infections and 2 cases of osteitis pubis, but we have never had any liver or bone marrow damage.

Anything that has to do with the atom or the smashing of the atom has become a very romantic thing. You are going to inject radioactive material and kill a cancer. As a result, therefore, a lot of men are injecting these isotopes all over the country, and they don't know what they're doing.

I think an organization like this and men like ourselves, who are teachers and who stand for what's right and true, should be very, very critical of all these things.

Now, Rubin, I'm sure, is critical of his own work, but like every father he

thinks his child is the best, and he's very enthusiastic, and I think that somebody has to cool these enthusiastic people off once in a while.

DR. RUBIN FLOCKS (Iowa City, Iowa): I thank Dr. O'Conor for his discussion. I think it's very, very apropos, but I do think that the question of volume is important.

If you have a bag or a piece of tissue—or let's say it's a bag with a capsule around it—and the bag is full of tissue, I don't know how we can expect to add more material to the thing without breaking the capsule.

Assume this is the colloidal material. (Illustrating) As this fluid went through the thing, our original idea was that these dots would precipitate out as they touched the tissue. That's what we assumed. So, as the volume was increased the water would wash out and these little dots would precipitate out. But apparently they don't; and therefore, if you increase the volume you break this capsule, or the vessel walls and the material gets into the bloodstream or into the fascial planes, and you have got, instead of 20 millicuries of activity, say, 5 millicuries of activity in the prostate where one wishes it.

What we're doing is using the same amount of activity, but with a small volume and many little injections, hoping thus that the total number of millicuries that stay behind is greater than it would be the other way.

DR. O'CONOR: May I answer again? I don't know what difference there is between breaking the capsule on the way in or on the way out, because it's all the same thing.